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=> s promoter conversion

L1 6 PROMOTER CONVERSION

=> d 1-6 bib ab

L1 ANSWER 1 OF 6 MEDLINE
AN 1998088888 MEDLINE
DN 98088888
TI Inducible expression of p21WAF-1/CIP-1/SDI-1 from a **promoter conversion** retroviral vector.
AU Mrochen S; Klein D; Nikol S; Smith J R; Salmons B; Gunzburg W H
CS Institute of Molecular Virology, GSF-National Research Center for

Environment and Health, Universitat Munchen, Germany.
SO JOURNAL OF MOLECULAR MEDICINE, (1997 Nov-Dec) 75 (11-12) 820-8.
Journal code: B8C. ISSN: 0946-2716.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199804
EW 19980402
AB Constitutive, high-level expression of the potentially therapeutic WAF-1/CIP-1/SDI-1 gene is incompatible with cell growth. A **promoter conversion** retroviral vector carrying the WAF-1/CIP-1/SDI-1 gene under the transcriptional control of the glucocorticoid inducible promoter of mouse mammary tumor virus was used to infect human bladder carcinoma or feline kidney cells. Reduced cell growth due to a greater proportion of cells being in the G0/G1 phase of the cell cycle was observed when WAF-1/CIP-1/SDI-1 expression was activated by addition of glucocorticoid hormone. This system demonstrates the potential long-term therapeutic use of WAF-1/CIP-1/SDI-1 delivered by retroviral vectors for inhibiting the growth of rapidly proliferating cells. Moreover, the conditional expression of genes such as WAF-1/CIP-1/SDI-1 from such retroviral vectors may facilitate analysis of their function.

L1 ANSWER 2 OF 6 MEDLINE
AN 96228295 MEDLINE
DN 96228295
TI Importance of low affinity Elf-1 sites in the regulation of lymphoid-specific inducible gene expression.
AU John S; Marais R; Child R; Light Y; Leonard W J
CS Laboratory of Molecular Immunology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO JOURNAL OF EXPERIMENTAL MEDICINE, (1996 Mar 1) 183 (3) 743-50.
Journal code: I2V. ISSN: 0022-1007.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199609
AB Elf-1 is an Ets family transcription factor that regulates a number of inducible lymphoid-specific genes, including those encoding interleukin 3 (IL-3), granulocyte/macrophage colony-stimulating factor (GM-CSF), and the IL-2 receptor (IL-2R) alpha chain. A minimal oligonucleotide spanning the IL-2R alpha Elf-1 site (-97/-84) bound Elf-1 poorly, but binding activity markedly increased when this oligonucleotide was multimerized or flanking sequences were added. This result is consistent with the requirement of accessory proteins for efficient Elf-1 binding, as has been demonstrated for the GM-CSF and IL-3 promoters. A binding site selection analysis revealed the optimal Elf-1 consensus motif to be A(A/t)(C/a)CCGGAAGT(A/S), which is similar to the consensus motif for the related Drosophila E74 protein. This minimal high affinity site could bind Elf-1 and functioned as a stronger transcription element than the -97/-84 IL-2R alpha oligonucleotide when cloned upstream of a heterologous promoter. In contrast, in the context of the IL-2R alpha **promoter**, **conversion** of the naturally occurring low affinity Elf-1 site to an optimal site decreased inducible activation of a reporter construct in Jurkat

cells. This finding may be explained by the observation that another Ets family protein, ER GB/Fli-1, can efficiently bind only to the optimal site, and in this context, interferes with Elf-1 binding. Therefore, high affinity Elf-1 sites may lack sufficient binding specificity, whereas naturally occurring low affinity sites presumably favor the association of Elf-1 in the context of accessory proteins. These findings offer an explanation for the lack of optimal sites in any of the known Elf-1-regulated genes.

L1 ANSWER 3 OF 6 MEDLINE
AN 93113085 MEDLINE
DN 93113085
TI Conversion of dethiobiotin to biotin in cell-free extracts of Escherichia coli.
AU Ifuku O; Kishimoto J; Haze S; Yanagi M; Fukushima S
CS Shiseido Research Center, Yokohama, Japan..
SO BIOSCIENCE, BIOTECHNOLOGY, AND BIOCHEMISTRY, (1992 Nov) 56 (11) 1780-5.
Journal code: BDP. ISSN: 0916-8451.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS B
EM 199304
AB We constructed the plasmid pTTB151 in which the E. coli bioB gene was expressed under the control of the tac **promoter**. **Conversion** of dethiobiotin to biotin was demonstrated in cell-free extracts of E. coli carrying this plasmid. The requirements for this biotin-forming reaction included fructose-1,6-bisphosphate, Fe2+, S-adenosyl-L-methionine, NADPH, and KCl, as well as dethiobiotin as the substrate. The enzymes were partially purified from cell-free extracts by a procedure involving ammonium sulfate fractionation. Our results suggest that an unidentified enzyme(s) besides the bioB gene product is obligatory for the conversion of dethiobiotin to biotin.

L1 ANSWER 4 OF 6 BIOSIS COPYRIGHT 1998 BIOSIS
AN 98:76483 BIOSIS
DN 01076483
TI Inducible expression of p21-WAF-1-CIP-1-SDI-1 from a **promoter conversion** retroviral vector.
AU Mrochen S; Klein D; Nikol S; Smith J R; Salmons B; Guenzburg W H
CS Inst. Virol., Univ. Veterinary Sci., Josef-Baumann-Gasse 1, A-1210 Vienna, Austria
SO Journal of Molecular Medicine (Berlin) 75 (11-12). 1997. 820-828.
ISSN: 0946-2716
LA English
AB Constitutive, high-level expression of the potentially therapeutic WAF-1/CIP-1/SDI-1 gene is incompatible with cell growth. A **promoter conversion** retroviral vector carrying the WAF-1/CIP-1/SDI-1 gene under the transcriptional control of the glucocorticoid inducible promoter of mouse mammary tumor virus was used to infect human bladder carcinoma or feline kidney cells. Reduced cell growth due to a greater proportion of cells being in the G-0/G-1 phase of the cell cycle was observed when WAF-1/CIP-1/SD1-expression was activated by addition of glucocorticoid hormone. This system demonstrates the potential long-term therapeutic use of WAF-1/CIP-1/SDI-1 delivered by retroviral vectors for inhibiting the growth of rapidly proliferating cells. Moreover, the conditional expression of genes such as

WAF-1/CIP-1/SDI-1 from such retroviral vectors may facilitate analysis of their function.

L1 ANSWER 5 OF 6 BIOSIS COPYRIGHT 1998 BIOSIS
AN 96:238164 BIOSIS
DN 98786293
TI Importance of low affinity Elf-1 sites in the regulation of lymphoid-specific inducible gene expression.
AU John S; Marais R; Child R; Light Y; Leonard W J
CS Lab. Molecular Immunology, Natl. Heart, Lung, and Blood Inst., Natl. Inst. Health, Bethesda, MD 20892, USA
SO Journal of Experimental Medicine 183 (3). 1996. 743-750. ISSN: 0022-1007
LA English
AB Elf-1 is an Ets family transcription factor that regulates a number of inducible lymphoid-specific genes, including those encoding interleukin 3 (IL-3), granulocyte/macrophage colony-stimulating factor (GM-CSF), and the IL-2 receptor (IL-2R) alpha chain. A minimal oligonucleotide spanning the IL-2-alpha Elf-1 site (-97/-84) bound Elf-1 poorly, but binding activity markedly increased when this oligonucleotide was multimerized or flanking sequences were added. This result is consistent with the requirement of accessory proteins for efficient Elf-1 binding, as has been demonstrated for the GM-CSF and IL-3 promoters. A binding site selection analysis revealed the optimal Elf-1 consensus motif to be A(A/t)(C/a)CCGGAAGT(A/S), which is similar to the consensus motif for the related Drosophila E74 protein. This minimal high affinity site could bind Elf-1 and functioned as a stronger transcription element than the -97/-84 IL2R-alpha oligonucleotide when cloned upstream of a heterologous promoter. In contrast, in the context of the IL-2R-alpha **promoter**, **conversion** of the naturally occurring low affinity Elf-I site to an optimal site decreased inducible activation of a reporter construct in Jurkat cells. This finding may be explained by the observation that another Ets family protein, ERGB/Fli-1, can efficiently bind only to the optimal site, and in this context, interferes with Elf-1 binding. Therefore, high affinity Elf-1 sites may lack sufficient binding specificity, whereas naturally occurring low affinity sites presumably favor the association of Elf-1 in the context of accessory proteins. These findings offer an explanation for the lack of optimal sites in any of the known Elf-1-regulated genes.

L1 ANSWER 6 OF 6 BIOSIS COPYRIGHT 1998 BIOSIS
AN 93:168763 BIOSIS
DN BA95:89813
TI CONVERSION OF DETHIOBIOTIN TO BIOTIN IN CELL-FREE EXTRACTS OF ESCHERICHIA-COLI.
AU IFUKU O; KISHIMOTO J; HAZE S-I; YANAGI M; FUKUSHIMA S
CS SHISEIDO RES. CENT., 1050, NIPPA-CHO, KOHOKU-KU, YOKOHAMA 223, JAPAN.
SO BIOSCI BIOTECHNOL BIOCHEM 56 (11). 1992. 1780-1785. CODEN: BBBIEJ
LA English
AB We constructed the plasmid pTTB151 in which are E. coli bioB gene was expressed under the control of the tac **promoter**. **Conversion** of dethiobiotin to biotin was demonstrated in cell-free extracts of E. coli carrying this plasmid. The requirements for this biotin-forming reaction included fructose-1,6-bisphosphate, Fe2+, S-adenosyl-L-methione, NADPH, and KCl, a well as dethiobiotin as the substrate. The enzymes were partially purified from cell-free extracts by a procedure involving ammonium sulfate fractionation. Our results suggest that an unidentified enzyme(s) besides the bioB gene

product is obligatory for the conversion of dethiobiotin in biotin.

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=> s self inactivating and retrovir?

L1          43 SELF INACTIVATING AND RETROVIR?

=> s l1 range=,1994

L2          24 L1

=> d 1-10 bib ab


L2   ANSWER 1 OF 24  MEDLINE
AN   93211392     MEDLINE
DN   93211392
```

TI Stable expression of antibiotic resistance genes using a promoter fragment of the U1 snRNA gene.
AU Asselbergs F A; Pronk R
CS Biotechnology Department, CIBA-GEIGY Ltd., Basle, Switzerland..
SO MOLECULAR BIOLOGY REPORTS, (1993 Feb) 17 (2) 101-14.
Journal code: NGW. ISSN: 0301-4851.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199307
AB As U1 snRNA is produced in all mammalian cell types, antibiotic resistance genes driven by this promoter would be ideally suited as genetic selection markers. However, although the U1 snRNA gene is transcribed by RNA polymerase II, its native product is not a messenger RNA, but a splicing cofactor. To test whether this promoter could nevertheless produce a functional mRNA, sensitive reporter genes expressing resistance to the antibiotics hygromycin-B and bleomycin were constructed with either the U1 snRNA promoter or the SV40 early promoter. Resistant cell lines could only be obtained with constructs equipped with a functional polyadenylation signal. With the U1 snRNA promoter about three times fewer colonies were obtained than with the SV40 early promoter. Another potential advantage of the U1 snRNA promoter is that, in contrast to the promoters commonly used to express genetic selection markers, the enhancer-like element contained in the U1 snRNA promoter had only a minimal stimulative effect, only detectable with the most sensitive methods, on an adjacent mRNA-producing gene. The U1 snRNA promoter was also capable of expressing bleomycin resistance in the context of a **self-inactivating retrovirus** vector, whereby it was discovered that the mouse 3T3 cells used in this experiment were 10 times more sensitive to bleomycin than human or hamster cell lines.

L2 ANSWER 2 OF 24 MEDLINE
AN 93139782 MEDLINE
DN 93139782
TI Importance of 3' non-coding sequences for efficient **retrovirus**-mediated gene transfer in avian cells revealed by **self-inactivating** vectors.
AU Flamant F; Aubert D; Legrand C; Cosset F L; Samarut J
CS Laboratoire de Biologie Moleculaire et Cellulaire, INRA-CNRS UMR 49, France.
SO JOURNAL OF GENERAL VIROLOGY, (1993 Jan) 74 (Pt 1) 39-46.
Journal code: I9B. ISSN: 0022-1317.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199304
AB Avian leukosis virus-derived vectors were constructed with an internal transcriptional promoter and various 3' non-coding sequences. Deletions were introduced into the downstream U3 long terminal repeat (LTR) to obtain self-inactivation of LTR-mediated transcription after one round of replication. However, 3' non-coding sequences appeared to determine not only self-inactivation of the vectors but also gene transfer efficiency. Further analysis revealed the influence of these sequences on both internal gene expression and RNA packaging. One construct permitted gene transfer while inactivating 5' LTR-promoted transcription.

L2 ANSWER 3 OF 24 MEDLINE
AN 93114447 MEDLINE
DN 93114447
TI An improved **retroviral** vector for assaying promoter activity. Analysis of promoter interference in pIP211 vector.
AU Nakajima K; Ikenaka K; Nakahira K; Morita N; Mikoshiba K
CS Institute for Protein Research, Osaka University, Japan..
SO FEBS LETTERS, (1993 Jan 4) 315 (2) 129-33.
Journal code: EUH. ISSN: 0014-5793.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199304
AB We recently developed a novel promoter assay system using a **retroviral** vector (pIP200 series). Transcription from the internal promoter, which had been inserted for the promoter assay, was shown to be interfered with by transcription from the upstream long terminal repeat (LTR). Here we report a new high-titer '**self-inactivating**' vector, in which transcription interference was virtually eliminated. This new vector was constructed by introducing only a very minor mutation into the 'TATA box' in the 3'-LTR. This mutation was successfully transferred to the 5'-LTR after reverse transcription, yielding a provirus incapable of transcribing viral RNA. The viral titer was not reduced by the mutation, permitting general application of this virus.

L2 ANSWER 4 OF 24 MEDLINE
AN 91255559 MEDLINE
DN 91255559
TI MoMuLV-derived **self-inactivating** **retroviral** vectors possessing multiple cloning sites and expressing the resistance to either G418 or hygromycin B.
AU Marty L; Roux P; Royer M; Piechaczyk M
CS Laboratoire de Biologie Moleculaire, URA CNRS 1191 Genetique Moleculaire, Montpellier, France..
SO BIOCHIMIE, (1990 Dec) 72 (12) 885-7.
Journal code: A14. ISSN: 0300-9084.
CY France
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199109
AB To facilitate cloning procedures in recombinant murine leukemia virus-derived **retroviruses**, we have constructed vectors that both carry a polylinker with multiple restriction sites and express resistance to either G418 or hygromycin B. Our vectors are **self-inactivating** **retroviruses** that suppress interferences between LTR enhancers and internal promoters and avoid transcriptional stimulation of host cell genes. They can also be used as expression vectors in direct transfection assays, since no translation initiation codon lies between the 5' LTR and the cloning polylinker.

L2 ANSWER 5 OF 24 MEDLINE
AN 91202569 MEDLINE
DN 91202569
TI Promoter interactions in **retrovirus** vectors introduced into fibroblasts and embryonic stem cells.

AU Soriano P; Friedrich G; Lawinger P
CS Howard Hughes Medical Institute, Baylor College of Medicine, Houston, Texas 77030.
NC RR05425 (NCRR)
RO1-HD24875 (NICHD)
SO JOURNAL OF VIROLOGY, (1991 May) 65 (5) 2314-9.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199107
AB The activity of the Moloney murine leukemia virus promoter is restricted in mouse embryonic stem cells. Gene expression with **retrovirus** vectors can be achieved in these cells if internal promoters are used. To address the possible influence of the viral enhancer sequences on expression from the internal promoter, we have constructed high-titer, **self-inactivating retrovirus** vectors which delete viral regulatory sequences upon integration in the host genome. We show that deleting most of the viral enhancer sequences has no significant effect on viral titer. This enhancer deletion leads to either an increase or a decrease in the amount of RNA transcribed from the internal promoter, but no consistent change can be found with any type of vector. The same changes in expression from the internal promoter observed in embryonic stem cells are also observed in 3T3 fibroblast cells, in which the viral promoter is active. These results indicate that viral regulatory elements influence expression from an internal promoter independently of expression from the virus promoter.

L2 ANSWER 6 OF 24 MEDLINE
AN 91201400 MEDLINE
DN 91201400
TI Inhibition of proliferation of primary avian fibroblasts through expression of histone H5 depends on the degree of phosphorylation of the protein.
AU Aubert D; Garcia M; Benchaibi M; Poncet D; Chebloune Y; Verdier G; Nigon V; Samarut J; Mura C V
CS Laboratoire de Biologie Moleculaire et Cellulaire, UMR 13 Centre National de la Recherche Scientifique, Lyon, France.
SO JOURNAL OF CELL BIOLOGY, (1991 May) 113 (3) 497-506.
Journal code: HMV. ISSN: 0021-9525.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199107
AB To obtain stable and constitutive expression of histone H5 at levels comparable to those observed in normal chicken erythrocytes, an avian **self-inactivating retroviral** vector was used to transfer the H5 gene into cells which do not express this protein. The vector, pDAH5, was obtained by removing the CAAT and TATA boxes of the 3'LTR of the avian leukosis virus RAV-2 and inserting the H5 sequence. Infection of QT6 quail cells with the recombinant virus (DAH5) led to the stable integration of the foreign H5 gene at low copy number, to the formation of correctly initiated mRNA transcripts and to the production of H5 protein. The amount of H5 expressed was equivalent to that of a mature chicken erythrocyte. Expression of histone H5 in DAH5

transformed cells, such as QT6 or AEV-ES4, transformed chicken embryo fibroblasts had only slight effects on the growth rate and did not inhibit cell replication. Conversely, the effect of H5 expression on normal quail and chicken fibroblasts was dramatic: cells acquired the aspect of quiescent fibroblasts, grew very slowly, and nuclei looked compacted, often extruded from the cell. The H5 histone produced in QT6-transformed cells was found to be phosphorylated while in normal chicken fibroblasts the protein lacked this posttranslational modification. It is proposed that the chromatin-condensing role of histone H5 is inhibited by its phosphorylation.

L2 ANSWER 7 OF 24 MEDLINE
AN 90355975 MEDLINE
DN 90355975
TI Functional analysis and nucleotide sequence of the promoter region of the murine hck gene.
AU Lock P; Stanley E; Holtzman D A; Dunn A R
CS Ludwig Institute for Cancer Research, Melbourne Tumour Biology Branch, Parkville, Victoria, Australia.
SO MOLECULAR AND CELLULAR BIOLOGY, (1990 Sep) 10 (9) 4603-11.
Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-M34946
EM 199011
AB The structure and function of the promoter region and exon 1 of the murine hck gene have been characterized in detail. RNase protection analysis has established that hck transcripts initiate from heterogeneous start sites located within the hck gene. Fusion gene constructs containing hck 5'-flanking sequences and the bacterial Neor gene have been introduced into the hematopoietic cell lines FDC-P1 and WEHI-265 by using a **self-inactivating retroviral** vector. The transcriptional start sites of the fusion gene are essentially identical to those of the endogenous hck gene. Analysis of infected WEHI-265 cell lines treated with bacterial lipopolysaccharide (LPS) reveals a 3- to 5-fold elevation in the levels of endogenous hck mRNA and a 1.4- to 2.6-fold increase in the level of Neor fusion gene transcripts, indicating that hck 5'-flanking sequences are capable of conferring LPS responsiveness on the Neor gene. The 5'-flanking region of the hck gene contains sequences similar to an element which is thought to be involved in the LPS responsiveness of the class II major histocompatibility gene A alpha k. A subset of these sequences are also found in the 5'-flanking regions of other LPS-responsive genes. Moreover, this motif is related to the consensus binding sequence of NF-kappa B, a transcription factor which is known to be regulated by LPS.

L2 ANSWER 8 OF 24 MEDLINE
AN 90269622 MEDLINE
DN 90269622
TI Construction and hormone regulation of a novel **retroviral** vector.
AU Mee P J; Brown R
CS CRC Department of Medical Oncology, Glasgow University, U.K.
SO GENE, (1990 Apr 16) 88 (2) 289-92.
Journal code: FOP. ISSN: 0378-1119.
CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199009
AB We report the analysis of a **self-inactivating** **retroviral** vector, constructed to allow inducible gene expression of inserted sequences from the mouse mammary tumour virus hormonal response element. The cloning strategy has been designed to allow for ease of insertion of the genes of interest. The vector contains the aph gene, allowing geneticin-resistance selection in mammalian cells. We have characterised dexamethasone (Dex)-induced increase in gene expression using the reporter gene encoding chloramphenicol acetyltransferase (CAT) inserted into the **retroviral** vector. We observe low basal levels of CAT activity in infected cells which is increased up to 50-fold by induction with Dex. The induction of pooled clones is 13.3-fold. Variation in Dex-induced CAT activity is observed in independently infected clones, which is not explained by proviral copy number.

L2 ANSWER 9 OF 24 MEDLINE
AN 90014804 MEDLINE
DN 90014804
TI Germ line c-myc is not down-regulated by loss or exclusion of activating factors in myc-induced macrophage tumors.
AU Mango S E; Schuler G D; Steele M E; Cole M D
CS Lewis Thomas Laboratory, Department of Biology, Princeton University, New Jersey 08544-1014..
SO MOLECULAR AND CELLULAR BIOLOGY, (1989 Aug) 9 (8) 3482-90. Journal code: NGY. ISSN: 0270-7306.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-M28065; GENBANK-M28066
EM 199001
AB As in tumors with c-myc chromosomal translocations, c-myc **retrovirus**-induced monocyte tumors constitutively express an activated form of c-myc (the proviral gene), whereas the normal endogenous c-myc genes are transcriptionally silent. Treatment of these **retrovirus**-induced tumor cells with a number of bioactive chemicals and growth factors that are known to induce c-myc expression in cells of the monocyte lineage failed to induce the endogenous c-myc gene. In contrast, the same treatments induced the c-fos gene in both tumors and a control macrophage line. To investigate c-myc suppression further, a normal copy of the human c-myc gene was introduced into tumor and control cell lines by using a **retrovirus** with **self-inactivating** long terminal repeats. This transduced normal gene was expressed at equivalent levels in all cells, regardless of the state of endogenous c-myc gene expression, and was strongly induced by agents that induce the normal gene in the control cells. These results indicate that the signal transduction pathways that normally activate the c-myc gene are functional in myc-induced tumor cells and suggest that endogenous c-myc is actively suppressed. An examination of the c-myc locus itself showed that the lack of transcriptional activity correlated with the absence of several prominent DNase I-hypersensitive sites in the 5'-flanking region of the gene but without loss of general DNase sensitivity. Furthermore, analysis of 22 methylation-sensitive restriction enzyme sites in the 5'-flanking region, first exon, and first intron indicated that the

silent c-myc genes remained in the same unmethylated state as did actively expressed genes. Thus, c-myc suppression does not appear to result from the most frequently described mechanisms of gene inactivation.

L2 ANSWER 10 OF 24 MEDLINE
AN 89315828 MEDLINE
DN 89315828
TI Analysis of mammalian cell genetic regulation in situ by using **retrovirus**-derived "portable exons" carrying the Escherichia coli lacZ gene.
AU Brenner D G; Lin-Chao S; Cohen S N
CS Department of Genetics, Stanford University School of Medicine, CA 94305-5120.
NC GM 27241 (NIGMS)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1989 Jul) 86 (14) 5517-21.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198910
AB **Self-inactivating** derivatives of Moloney murine leukemia **retrovirus** containing the Escherichia coli lacZ gene were used to detect and study the regulation of transcription initiated at chromosomally located promoters in mouse fibroblasts. The introduction of splice acceptor sites in all three translational reading frames relative to lacZ and the inclusion of an in-frame ATG translation start codon in one construct allowed synthesis of beta-galactosidase fusion proteins upon insertion of **retrovirus** vectors containing lacZ into introns 3' to either protein-coding or noncoding exons. Selection of lacZ-expressing cells by fluorescence-activated cell sorting and the analysis of beta-galactosidase production after serum deprivation has yielded lines in which lacZ was fused to genes induced by growth arrest in the G0 state.

=> d 11-24 bib ab

L2 ANSWER 11 OF 24 MEDLINE
AN 86205863 MEDLINE
DN 86205863
TI **Self-inactivating retroviral** vectors designed for transfer of whole genes into mammalian cells.
AU Yu S F; von Ruden T; Kantoff P W; Garber C; Seiberg M; Ruther U; Anderson W F; Wagner E F; Gilboa E
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1986 May) 83 (10) 3194-8.
Journal code: PV3. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198608
AB A **retrovirus**-derived vector called **self-inactivating** (SIN) vector was designed for the transduction of whole genes into mammalian cells. SIN vectors contain a deletion of 299 base pairs in the 3' long terminal repeat (LTR), which

includes sequences encoding the enhancer and promoter functions. When viruses derived from such vectors were used to infect NIH 3T3 cells, the deletion was transferred to the 5' LTR, resulting in the transcriptional inactivation of the provirus in the infected cell. Introduction of a hybrid gene (human metallothionein-promoted c-fos) into cells via a SIN vector was not associated with rearrangements and led to the formation of an authentic mRNA transcript, which in some cases was induced by cadmium. SIN vectors should be particularly useful in gene transfer experiments designed to study the regulated expression of genes in mammalian cells. Absence of enhancer and promoter sequences in both LTRs of the integrated provirus should also minimize the possibility of activating cellular oncogenes and may provide a safer alternative to be used in human gene therapy.

L2 ANSWER 12 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 94:545441 BIOSIS
DN 98004989
TI Improved **self-inactivating retroviral** vectors derived from spleen necrosis virus.
AU Olson P; Nelson S; Dornburg R
CS Dep. Molecular Genetics Microbiol., Robert Wood Johnson Med. Sch., Univ. Medicine Dentistry New Jersey, 675 Hoes Lane, Piscataway, NJ 08854, USA
SO Journal of Virology 68 (11). 1994. 7060-7066. ISSN: 0022-538X
LA English
AB **Self-inactivating** (SIN) **retroviral** vectors contain a deletion spanning most of the right long terminal repeat's (LTR's) U3 region. Reverse transcription copies this deletion to both LTRs. As a result, there is no transcription from the 5' LTR, preventing further replication Many previously developed SIN vectors, however, had reduced titers or were genetically unstable. Earlier, we reported that certain SIN vectors derived from spleen necrosis virus (SNV) experienced reconstitution of the U3-deleted LTR at high frequencies. This reconstitution occurred on the DNA level and appeared to be dependent on defined vector sequences. To study this phenomenon in more detail, we developed an almost completely U3-free **retroviral** vector. The promoter and enhancer of the left LTR were replaced with those of the cytomegalovirus immediate-early genes. This promoter swap did not impair the level of transcription or alter its start site. Our data indicate that SNV contains a strong initiator which resembles that of human immunodeficiency virus. We show that the vectors replicate with efficiencies similar to those of vectors possessing two wild-type LTRs. U3-deleted vectors carrying the hygromycin B phosphotransferase gene did not observably undergo LTR reconstitution, even when replicated in helper cells containing SNV-LTR sequences. However, vectors carrying the neomycin resistance gene did undergo LTR reconstitution with the use of homologous helper cell LTR sequences as template. This supports our earlier finding that sequences within the neomycin resistance gene can trigger recombination.

L2 ANSWER 13 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 93:251520 BIOSIS
DN BA95:130695
TI STABLE EXPRESSION OF ANTIBIOTIC RESISTANCE GENES USING A PROMOTER FRAGMENT OF THE U1 SNRNA GENE.
AU ASSELBERGS F A M; PRONK R
CS BIOTECHNOLOGY DEP., CIBA-GEIGY LTD., K681-442 CH-4002 BASLE, SWITZ.
SO MOL BIOL REP 17 (2). 1993. 101-114. CODEN: MLBRBU ISSN: 0301-4851

LA English
AB As U1 snRNA is produced in all mammalian cell types, antibiotic resistance genes driven by this promoter would be ideally suited as genetic selection markers. However, although the U1 snRNA gene is transcribed by RNA polymerase II, its native product is not a messenger RNA, but a splicing cofactor. To test whether this promoter could nevertheless produce a functional mRNA, sensitive reporter genes expressing resistance to the antibiotics hygromycin-B and bleomycin was constructed with either the U1 snRNA promoter or the SV40 early promoter. Resistant cell lines could only be obtained with constructs equipped with a functional polyadenylation signal. With the U1 snRNA promoter about three times fewer colonies were obtained than with the SV40 promoter. Another potential advantage of the U1 snRNA promoter is that, in contrast to the promoter commonly used to express genetic selection markers, the enhancer-like element contained in the U1 snRNA promoter had only a minimal stimulative effect, only detectable with the most sensitive methods, on an adjacent mRNA-producing gene. The U1 snRNA promoter may also capable of expressing bleomycin resistance in the context of a **self -inactivating retrovirus** vector, whereby it was discovered that the mouse 3T3 cells used in this experiment were 10 times more sensitive to bleomycin than human or hamster cell lines.

L2 ANSWER 14 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 93:164489 BIOSIS
DN BA95:85539
TI IMPORTANCE OF 3' NON-CODING SEQUENCES FOR EFFICIENT **RETROVIRUS**-MEDIATED GENE TRANSFER IN AVIAN CELLS REVEALED BY **SELF-INACTIVATING** VECTORS.
AU FLAMANT F; AUBERT D; LEGRAND C; COSSET F-L; SAMARUT J
CS LAB. DE BIOL. MOL. CELLULAIRE, INRA-CNRS UMR 49, ECOLE NORMALE SUPERIEURE DE LYON, 46 ALLEE ITALIE, 69364 LYON CEDEX 07, FR.
SO J GEN VIROL 74 (1). 1993. 39-46. CODEN: JGVIAY ISSN: 0022-1317
LA English
AB Avian leukosis virus-derived vectors were constructed with an internal transcriptional promoter and various 3' non-coding sequences. Deletions were introduced into the downstream U3 long terminal repeat (LTR) to obtain self-inactivation of LTR-mediated transcription after one round of replication. However, 3' non-coding sequences appeared to determine not only self-inactivation of the vectors but also gene transfer efficiency. Further analysis revealed the influence of these sequences on both internal gene expression and RNA packaging. One construct permitted gene transfer while inactivating 5' LTR-promoted transcription.

L2 ANSWER 15 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 93:140830 BIOSIS
DN BA95:73630
TI AN IMPROVED **RETROVIRAL** VECTOR FOR ASSAYING PROMOTER ACTIVITY ANALYSIS OF PROMOTER INTERFERENCE IN PIP211 VECTOR.
AU NAKAJIMA K; IKENAKA K; NAKAHIRA K; MORITA N; MIKOSHIBA K
CS DIV. REGULATION MACROMOLECULAR FUNCTION, INST. PROTEIN RES., OSAKA UNIV., 3-2 YAMADAOKA, SUITA, OSAKA 565, JAPAN.
SO FEBS (FED EUR BIOCHEM SOC) LETT 315 (2). 1993. 129-133. CODEN: FEBLAL ISSN: 0014-5793
LA English
AB We recently developed a novel promoter assay system using a **retroviral** vector (pIP200 series). Transcription from the internal promoter, which had been inserted for the promoter assay, was shown to be interfered with by transcription from the upstream

long terminal repeat (LTR). Here we report a new high-titer '**self-inactivating**' vector, in which transcription interference was virtually eliminated. This new vector was constructed by introducing only a very minor mutation into the 'TATA box' in the 3'-LTR. This mutation was successfully transferred to the 5'-LTR after reverse transcription, yielding a provirus incapable of transcribing viral RNA. The viral titer was not reduced by the mutation, permitting general application of this virus.

L2 ANSWER 16 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 92:434312 BIOSIS
DN BA94:86437
TI GENE-SEARCH VIRUSES AND FACS-GAL PERMIT THE DETECTION ISOLATION AND CHARACTERIZATION OF MAMMALIAN CELLS WITH IN-SITU FUSIONS BETWEEN CELLULAR GENES AND ESCHERICHIA-COLI LACZ.
AU KERR W G; HERZENBERG L A
CS DEP. GENETICS, STANFORD UNIV. SCH. MED., STANFORD, CALIF. 94305.
SO METHODS (ORLANDO) 2 (3). 1991. 261-271. CODEN: MTHDE9 ISSN: 1046-2023
LA English
AB We describe **self-inactivating** **retroviruses** that will activate expression of the receptor gene, Escherichia coli lacZ, upon integration within a cellular gene (Gensr1) or near a cellular enhancer (Enhsr1), referred to collectively as gene-search viruses. If the Gensr1 virus integrates within an intron of a gene, splicing of a lacZ neo-exon to an upstream cellular exon can occur, resulting in transcriptional and translational fusion between E. coli lacZ and a cellular gene. The Enhsr1 **retrovirus** generates a provirus that lacks the LTR enhancer region and thus is dependent upon flanking cellular enhancers to activate expression of lacZ. Fluorescence-activated cell sorting permits mammalian cells infected with the gene-search viruses that contain gene fusions between lacZ and cellular transcription control elements to be isolated as a population or as clones of single cells. Clones can be analyzed via a rapid, sensitive assay for .beta.-galactosidase activity carried out in 96-well plates, permitting clones with integrations in conditionally expressed genes to be identified. This approach has led to isolation of gene-search virus integrations in developmentally regulated genes and loci. In addition, lacZ+ clones derived from Gensr1 infections can be screened via a histochemical stain (X-gal) for subcellular targetting of .beta.-gal activity. Molecular characterization of such Gensr1 integrations could allow identification of mammalian proteins with specific subcellular localizations. Finally, we demonstrate the potential of gene-search viruses for obtaining expression of lacZ in normal cells both in vitro and in vivo.

L2 ANSWER 17 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 91:271386 BIOSIS
DN BA92:4001
TI PROMOTER INTERACTIONS IN **RETROVIRUS** VECTORS INTRODUCED INTO FIBROBLASTS AND EMBRYONIC STEM CELLS.
AU SORIANO P; FRIEDRICH G; LAWINGER P
CS HOWARD HUGHES MEDICAL INSTITUTE, BAYLOR COLLEGE MEDICINE, HOUSTON, TEX. 77030.
SO J VIROL 65 (5). 1991. 2314-2319. CODEN: JOVIAM ISSN: 0022-538X
LA English
AB The activity of the Moloney murine leukemia virus promoter is restricted in mouse embryonic stem cells. Gene expression with **retrovirus** vectors can be achieved in these cells if internal

promoters are used. To address the possible influence of the viral enhancer sequences on expression from the internal promoter, we have constructed high-titer, **self-inactivating retrovirus** vectors which delete viral regulatory sequences upon integration in the host genome. We show that deleting most of the viral enhancer sequences has no significant effect on viral titer. This enhancer deletion lead to either an increase or a decrease in the amount of RNA transcribed from the internal promoter, but no consistent change can be found with any type of vector. The same changes in expression from the internal promoter observed in embryonic stem cells are also observed in 3T3 fibroblast cells, in which the viral promoter is active. These results indicate that viral regulatory elements influence expression from an internal promoter independently of expression from the virus promoter.

L2 ANSWER 18 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 91:268135 BIOSIS
DN BA92:750
TI INHIBITION OF PROLIFERATION OF PRIMARY AVIAN FIBROBLASTS THROUGH EXPRESSION OF HISTONE H5 DEPENDS ON THE DEGREE OF PHOSPHORYLATION OF THE PROTEIN.
AU AUBERT D; GARCIA M; BENCHAIBI M; PONCET D; CHEBLOUNE Y; VERDIER G; NIGON V; SAMARUT J; MURA C V
CS LAB. DE BIOLOGIE MOLECULAIRE ET CELLULAIRE, UMR 13 CENTRE NATL. DE LA RECHERCHE SCIENTIFIQUE, ECOLE NORMALE SUPERIEURE DE LYON, 69364 LYHON CEDEX 07, FRANCE.
SO J CELL BIOL 113 (3). 1991. 497-506. CODEN: JCLBA3 ISSN: 0021-9525
LA English
AB To obtain stable and constitutive expression of histone H5 at levels comparable to those observed in normal chicken erythrocytes, an avian **self-inactivating retroviral** vector was used to transfer the H5 gene into cells which do not express this protein. The vector, pDAH5, was obtained by removing the CAAT and TATA boxes of the 3LTR of the avian leukosis virus RAV-2 and inserting the H5 sequence. Infection of QT6 quail cells with the recombinant virus (DAH5) led to the stable integration of the foreign H5 gene at low copy number, to the formation of correctly initiated mRNA trasncripts and to the production of H5 protein. The amount of H5 expressed was equivalent to that of a mature chicken erythrocyte. Expression of histone H5 in DAH5 transformed cells, such as QT6 or AEV-ES4, transformed chicken embryo fibroblasts had only slight effects on the growth rate and did not inhibit cell replication. Conversely, the effect of H5 expression on normal quail and chicken fibroblasts was dramatic: cells acquired the aspect of quiescent fibroblasts, grew very slowly, and nuclei looked compacted, often extruded from the cell. The H5 histone produced in QT6-transformed cells was found to be phosphorylated while in normal chicken fibroblasts the protein lacked this posttranslational modification. It is proposed that the chromatin-condensing role of histone H5 is inhibited by its phosphorylation.

L2 ANSWER 19 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 91:203428 BIOSIS
DN BA91:106653
TI MOMULV-DERIVED **SELF-INACTIVATING RETROVIRAL** VECTORS POSSESSING MULTIPLE CLONING SITES AND EXPRESSING THE RESISTANCE TO EITHER G418 OR HYGROMYCIN B.
AU MARTY L; POUX P; ROYER M; PIECHACZYK M
CS LAB. BIOLOGIE MOLECULAIRE, URA CNRS 1191, GENETIQUE MOLECULAIRE, USTL PLACE E BATAILLON 34095, MONTPELLIER, CEDEX 05.

SO BIOCHIMIE (PARIS) 72 (12). 1990. 885-888. CODEN: BICMBE ISSN: 0300-9084
LA English
AB To facilitate cloning procedures in recombinant murine leukemia virus-derived **retroviruses**, we have constructed vectors that both carry a polylinker with multiple restriction sites and express resistance to either G418 or hygromycin B. Our vectors are **self-inactivating retroviruses** that suppress interferences between LTR enhancers and internal promoters and avoid transcriptional stimulation of host cell genes. They can also be used as expression vectors in direct transfection assays, since no translation initiation codon lies between the 5' LTR and the cloning polylinker.

L2 ANSWER 20 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 90:471286 BIOSIS
DN BA90:110706
TI FUNCTIONAL ANALYSIS AND NUCLEOTIDE SEQUENCE OF THE PROMOTER REGION OF THE MURINE HCK GENE.
AU LOCK P; STANLEY E; HOLTZMANN D A; DUNN A R
CS LUDWIG INST. FOR CANCER RES., MELBOURNE TUMOUR BIOL. BRANCH, P.O. ROYAL MELBOURNE HOSP., PARKVILLE, VICTORIA 3050, AUST.
SO MOL CELL BIOL 10 (9). 1990. 4603-4611. CODEN: MCEBD4 ISSN: 0270-7306
LA English
AB The structure and function of the promoter region and exon 1 of the murine hck gene have been characterized in detail. RNase protection analysis has established that hck transcripts initiate from heterogeneous start sites located within the hck gene. Fusion gene constructs containing hck 5'-flanking sequences and the bacterial Neor gene have been introduced into the hematopoietic cell lines FDC-P1 and WEHI-265 by using a **self-inactivating retroviral** vector. The transcriptional start sites of the fusion gene are essentially identical to those of the endogenous hck gene. Analysis of infected WEHI-265 cell lines treated with bacterial lipopolysaccharide (LPS) reveals a 3- to 5-fold elevation in the levels of endogenous hck mRNA and a 1.4- to 2.6-fold increase in the level of Neor fusion gene transcripts, indicating that hck 5'-flanking sequences are capable of conferring LPS responsiveness on the Neor gene. The 5'-flanking region of the hck gene contains sequences similar to an element which is thought to be involved in the LPS responsiveness of the class II major histocompatibility gene A.alpha.k. A subset of these sequences are also found in the 5'-flanking regions of other LPS-responsive genes. Moreover, this motif is related to the consensus binding sequence of NF-kB, a transcription factor which is known to be regulated by LPS.

L2 ANSWER 21 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 90:331353 BIOSIS
DN BA90:39372
TI CONSTRUCTION AND HORMONE REGULATION OF A NOVEL **RETROVIRAL** VECTOR.
AU MEE P J; BROWN R
CS DEP. MED. ONCOL., BEATSON INST., GARSCUBE ESTATE, SWITCHBACK ROAD, BEARSDEN, GLASGOW G61 1BD, UK.
SO GENE (AMST) 88 (2). 1990. 289-292. CODEN: GENED6 ISSN: 0378-1119
LA English
AB We report the analysis of a **self-inactivating retroviral** vector, constructed to allow inducible gene expression of inserted sequences from the mouse mammary tumour virus hormonal response element. The cloning strategy has been designed to

allow for ease of insertion of the genes of interest. The vector contains the aph gene, allowing geneticin-resistance selection in mammalian cells. We have characterized dexamethasone (Dex)-induced increase in gene expression using the reporter gene encoding chloramphenicol acetyltransferase (CAT) inserted into the **retroviral** vector. We observe low basal levels of CAT activity in infected cells which is increased up to 50-fold by induction with Dex. The induction of pooled clones is 13.3-fold. Variation in Dex-induced CAT activity is observed in independently infected clones, which is not explained by proviral copy number.

L2 ANSWER 22 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 89:428478 BIOSIS
DN BA88:86736
TI GERM LINE C-MYC IS NOT DOWN-REGULATED BY LOSS OR EXCLUSION OF ACTIVATING FACTORS IN MYC-INDUCED MACROPHAGE TUMORS.
AU MANGO S E; SCHULER G D; STEELE M E R; COLE M D
CS LEWIS THOMAS LAB., DEP. BIOL., PRINCETON UNIV., PRINCETON, N.J. 08544-1014, USA.
SO MOL CELL BIOL 9 (8). 1989. 3482-3490. CODEN: MCEBD4 ISSN: 0270-7306
LA English
AB As in tumors with c-myc chromosomal translocations, c-myc **retrovirus**-induced monocyte tumors constitutively express an activated form of c-myc (the proviral gene), whereas the normal endogenous c-myc gene are transcriptionally silent. Treatment of these **retrovirus**-induced tumor cells with a number of bioactive chemicals and growth factors that are known to induce c-myc expression in cells of the monocyte lineage failed to induce the endogenous c-myc gene. In contrast, the same treatments induced the c-fos gene in both tumors and control macrophage line. To investigate c-myc suppression further, a normal copy of the human c-myc gene was introduced into tumor and control cell lines by using a **retrovirus** with **self-inactivating** long terminal repeats. This transduced normal gene was expressed at equivalent levels in all cells, regardless of the state of endogenous c-myc gene expression, and was strongly induced by agents that induce the normal gene in the control cells. The results indicate that the signal transduction pathways that normally activate the c-myc gene are functional in myc-induced tumor cells and suggest that endogenous c-myc is actively suppressed. An examination of the c-myc locus itself showed that the lack of transcriptional activity correlated with the absence of several prominant DNAse I-hypersensitive sites in the 5'-flanking region of the gene but without loss of general DNase sensitivity. Furthermore, analysis of 22 methylation-sensitive restriction enzymes sites in the 5'-flanking region, first exon, and first intron indicated that the silent c-myc genes remained in the same unmethylated state as did actively expressed genes. Thus, c-myc suppression does not appear to result from the most frequently described mechanism of gene inactivation.

L2 ANSWER 23 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 89:426460 BIOSIS
DN BA88:84718
TI ANALYSIS OF MAMMALIAN CELL GENETIC REGULATION IN SITU BY USING **RETROVIRUS**-DERIVED PORTABLE EXONS CARRYING THE ESCHERICHIA-COLI LAC-Z GENE.
AU BRENNER D G; LIN-CHAO S; COHEN S N
CS DEP. GENETICS, STANFORD UNIV. SCH. MED., STANFORD, CALIF. 94305-5120.
SO PROC NATL ACAD SCI U S A 86 (14). 1989. 5517-5521. CODEN: PNASA6 ISSN: 0027-8424

LA English
AB **Self-inactivating** derivatives of Moloney murine leukemia **retrovirus** containing the Escherichia coli lacZ gene were used to detect and study the regulation of transcription initiated at chromosomally located promoters in mouse fibroblasts. The introduction of splice acceptor sites in all three translational reading frames relative to lacZ and the inclusion of an in-frame ATG translation start codon in one construct allowed synthesis of .beta.-galactosidase fusion proteins upon insertion of **retrovirus** vectors containing lacZ into introns 3' to either protein-coding or noncoding exons. Selection of lacZ-expressing cells by fluorescence-activated cell sorting and the analysis of .beta.-galactosidase production after serum deprivation has yielded lines in which lacZ was fused to genes induced by growth arrest in the G0 state.

L2 ANSWER 24 OF 24 BIOSIS COPYRIGHT 1998 BIOSIS
AN 86:319674 BIOSIS
DN BA82:43979
TI **SELF-INACTIVATING RETROVIRAL** VECTORS DESIGNED FOR TRANSFER OF WHOLE GENES INTO MAMMALIAN CELLS.
AU YU S-F; VON RUDEN T; KANTOFF P W; GARBER C; SEIBERG M; RUTHER U; ANDERSON W F; WAGNER E F; GILBOA E
CS DEP. MOLECULAR BIOLOGY, PRINCETON UNIV., PRINCETON, NJ 08544.
SO PROC NATL ACAD SCI U S A 83 (10). 1986. 3194-3198. CODEN: PNASA6 ISSN: 0027-8424
LA English
AB A **retrovirus**-derived vector called **self-inactivating** (SIN) vector was designed for the transduction of whole genes into mammalian cells. SIN vectors contain a deletion of 299 base pairs in the 3' long terminal repeat (LTR), which includes sequences encoding the enhancer and promoter functions. When viruses derived from such vectors were used to infect NIH 3T3 cells, the deletion was transferred to the 5' LTR, resulting in the transcriptional inactivation of the provirus in the infected cell. Introduction of a hybrid gene (human metallothionein-promoted c-fos) into cells via a SIN vector was not associated with rearrangements and led to the formation of an authentic mRNA transcript, which in some cases was induced by cadmium. SIN vectors should be particularly useful in gene transfer experiments designed to study the regulated expression of genes in mammalian cells. Absence of enhancer and promoter sequences in both LTRs of the integrated provirus should also minimize the possibility of activating cellular oncogenes and may provide a safer alternative to be used in human gene therapy.

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=> s promoter conversion

         21637 PROMOTER
         17663 PROMOTERS
         28925 PROMOTER
                 (PROMOTER OR PROMOTERS)
        220980 CONVERSION
         19065 CONVERSIONS
        224113 CONVERSION
                 (CONVERSION OR CONVERSIONS)
L1          15 PROMOTER CONVERSION
                 (PROMOTER(W)CONVERSION)

=> s l1 and retrovir?

          3788 RETROVIR?
L2           0 L1 AND RETROVIR?

=> d 1 kwic

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L1            15 SEA FILE=USPAT PLU=ON  PROMOTER CONVERSION
L2             0 SEA FILE=USPAT PLU=ON  L1 AND RETROVIR?

=> d l1 kwic


US PAT NO:     5,723,641 [IMAGE AVAILABLE]            L1: 1 of 15

DETDESC:

DETD(79)

              TABLE

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Ex.   Promoter        Conversion %
                                Selectivity %
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23    ZnBr.sub.2      26          83
24    ZnI.sub.2       59          82
25    ZnCl.sub.2      64          76
26    ZnSO.sub.4      31.  .  .

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  * Patents News Folder under the Public Folders in e-mail for   *
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  *    related questions.                                         *
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  *    >>>>>>>>>>>>> NEW SUNDAY HOURS !!! <<<<<<<<<<<<<           *
  *                                                               *
  *    The APS is available:                                      *
  *            6:30am - 9:00pm Monday through Friday              *
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  *      APS is unavailable Thanksgiving Day, Christmas Day,      *
  *      and New Year's Day.                                      *
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FILE 'USPAT' ENTERED AT 13:05:20 ON 12 MAR 1998

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  *              W E L C O M E   T O   T H E                      *
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  *        U. S.   P A T E N T   T E X T   F I L E          *
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=> e gunzburg/in

E#      FILE            FREQUENCY  TERM
--      ----            ---------  ----
E1      USPAT                2      GUNZ, STEFAN/IN
E2      USPAT                1      GUNZBERG, GUY W/IN
E3      USPAT                0 --> GUNZBURG/IN
E4      USPAT                1      GUNZBURG, FRED/IN
E5      USPAT                1      GUNZEL, BODO/IN
E6      USPAT                1      GUNZEL, ERHARD P H/IN
E7      USPAT                1      GUNZEL, ERNST WERNER/IN
E8      USPAT                1      GUNZEL, HANS/IN
E9      USPAT                2      GUNZEL, PETER/IN
E10     USPAT               10      GUNZEL, RUDOLPH M JR/IN
E11     USPAT                2      GUNZELMAN, DEBORAH M/IN
E12     USPAT                1      GUNZELMANN, EDWARD J/IN

=> e

E13     USPAT                1      GUNZELMANN, KARL HEINZ/IN
E14     USPAT                5      GUNZENHAUSER, SIGMUND/IN
E15     USPAT                2      GUNZERT, WILLI/IN
E16     USPAT                1      GUNZI, KATUHIKO/IN
E17     USPAT                3      GUNZI, KOUICHI/IN
E18     USPAT                1      GUNZI, LAURENCE A/IN
E19     USPAT                1      GUNZI, THUTOMU/IN
E20     USPAT                1      GUNZIER, VOLKMAR/IN
E21     USPAT                1      GUNZINGER, ANTON/IN
E22     USPAT                1      GUNZLEN PUKALL, VOLKMAR/IN
E23     USPAT                8      GUNZLER PUKALL, VOLKMAR/IN
E24     USPAT                3      GUNZLER, THOMAS/IN

=> e saller/in

E#      FILE            FREQUENCY  TERM
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E1      USPAT                1      SALLENBACH, SHERRY K/IN
E2      USPAT                1      SALLENHAG, MARTIN/IN
E3      USPAT                0 --> SALLER/IN
E4      USPAT                3      SALLER, DONALD H/IN
E5      USPAT                4      SALLER, ERIK/IN
E6      USPAT                1      SALLER, FRANZ JOHN/IN
E7      USPAT                8      SALLER, HELMUT/IN
E8      USPAT                1      SALLER, HENRY A DECEASED/IN
E9      USPAT                5      SALLER, KENNETH R/IN
E10     USPAT                1      SALLER, LOUIS RICHARD/IN
E11     USPAT                1      SALLER, MICHAEL/IN
E12     USPAT                1      SALLER, STEPHEN W/IN

=> s e11

L1            1 "SALLER, MICHAEL"/IN

=> d bib
```

US PAT NO: 4,738,744 [IMAGE AVAILABLE] L1: 1 of 1
DATE ISSUED: Apr. 19, 1988
TITLE: One-sided corrugated board machine
INVENTOR: **Michael Saller**, Moosbach, Federal Republic of Germany
ASSIGNEE: BHS-Bayerische Berg-, Hutten- und Salzwerke Aktiengesellschaft, Federal Republic of Germany (foreign corp.)
APPL-NO: 07/097,493
DATE FILED: Sep. 16, 1987
ART-UNIT: 131
PRIM-EXMR: Jerome Massie
LEGAL-REP: Silverman, Cass, Singer & Winburn, Ltd.

=> s (homolog/ (3a) recombin?) (p) retrovir?

'HOMOLOG/ ' IS NOT A VALID FIELD CODE

=> s (homolog? (3a) recombin?) (p) retrovir?

24018 HOMOLOG?
32980 RECOMBIN?
3788 RETROVIR?
L2 67 (HOMOLOG? (3A) RECOMBIN?) (P) RETROVIR?

=> d 1-10 kwic

US PAT NO: 5,721,132 [IMAGE AVAILABLE] L2: 1 of 67

DETDESC:

DETD(8)

Vectors useful for practicing the present invention include plasmids, viruses (including phage), **retroviruses**, and integratable DNA fragments (i.e., fragments integratable into the host genome by **homologous recombination**). The vector replicates and functions independently of the host genome, or may, in some instances, integrate into the genome itself.. . .

US PAT NO: 5,716,832 [IMAGE AVAILABLE] L2: 2 of 67

SUMMARY:

BSUM(7)

There . . . several shortcomings in the current use of this approach. One issue involves the generation of "live virus" (i.e., competent replicating **retrovirus**) by the producer cell line. Preparations of human therapeutics which are contaminated with **retroviruses** are not currently considered suitable for use in human therapy. For example, extreme measures are taken to exclude **retroviral** contamination of monoclonal antibodies for imaging and therapy. Live virus can in conventional producer cells when: (1) The vector genome and the helper genomes recombine with each other; (2) The vector genome or helper genome **recombines** with **homologous** cryptic endogenous **retroviral** elements in the producer cell; or (3) Cryptic endogenous **retroviral** elements reactivate (e.g., xenotropic **retroviruses** in mouse cells).

SUMMARY:

BSUM(28)

Techniques for integrating a **retroviral** genome at a specific site in the DNA of a target cell involve the use of **homologous recombination**, or alternatively, the use of a modified integrase enzyme which will recognize a specific site on the target cell genome.. . .

DETDESC:

DETD(23)

Vector . . . and polytropic envelopes with the MoMLV gag/pol and with the vector makes these PCLs even less likely to generate replication-competent **retrovirus** by **homologous recombination** than amphotropic PCLs. Examples of the use of these methods are set forth below (see Example 2).

DETDESC:

DETD(34)

The most important safety concern for the production of **retroviral** vectors is the inherent propensity of **retroviral** PCLs to generate replication-competent **retrovirus** after introduction of a vector (Munchau et al., Virology 176:262-65, 1990). This can occur in at least two ways: 1) **homologous recombination** can occur between the therapeutic proviral DNA and the DNA encoding the MoMLV structural genes ("gag/pol" and "env") present in the PCL (discussed below under "Generation of PCLs"); and 2) generation of replication-competent virus by **homologous recombination** of the proviral DNA with the very large number of defective endogenous proviruses found in murine cells (Steffen and Weinberg,. . . Stephenson, Biochem. Biophys. Acta 458:323-54, 1976). Another safety concern with the utilization of murine cells for the production of murine **retroviral** vectors is the observation that some of the many endogenous proviral genes (**retrovirus**-like genes) in the murine genome are expressed, recognized by the **retroviral** structural gene products of murine PCLs, and delivered and expressed in target cells with an efficiency at least comparable to. . . Virol. 64:424-27, 1990). These observations strongly suggest that murine cell lines are an unsafe choice for the production of murine **retroviral** vectors for human therapeutics. To circumvent the inherent safety problems associated with murine cells, PCLs have been generated exclusively from. . .

US PAT NO: 5,716,826 [IMAGE AVAILABLE] L2: 3 of 67

SUMMARY:

BSUM(39)

Techniques for integrating a **retroviral** genome at a specific site in the DNA of a target cell involve the use of **homologous recombination**, or alternatively, the use of a modified integrase enzyme which will recognize a specific site on the target cell genome.. . .

DETDESC:

DETD(94)

In an eighth embodiment, the **retroviral** construct (with or without the expression of a palliative) provides a therapeutic effect by inserting itself into a virus, oncogene, or pathogenic gene, thereby inhibiting a function required for pathogenesis. This embodiment requires the direction of **retroviral** integration to a specific site in the genome by **homologous recombination**, integrase modification, or other methods (described below).

DETDESC:

DETD(250)

One technique for integrating an exogenous gene of a vector construct of a recombinant **retrovirus** into a specific site in a target cell's DNA employs **homologous recombination**. Plasmids containing sequences of DNA of greater than about 300 bp that are homologous to genomic sequences have been shown. . .

DETDESC:

DETD(251)

In order to employ **homologous recombination** in site-specific **retroviral** integration, a vector construct should be modified such that (a) homologous sequences (to the target cell's genome) are incorporated into. . . promoter. This approach has the effect of placing a region of homology near a potential free end of the double-stranded **retrovirus** vector genome. Free ends are known to increase the frequency of **homologous recombination** by a factor of approximately ten. In this approach, it may be necessary to defeat the normal mechanism of integration,. . .

US PAT NO: 5,716,613 [IMAGE AVAILABLE] L2: 4 of 67

SUMMARY:

BSUM(39)

Techniques for integrating a **retroviral** genome at a specific site in the DNA of a target cell involve the use of **homologous recombination**, or alternatively, the use of a modified integrase enzyme which will recognize a specific site on the target cell genome.. . .

DETDESC:

DETD(92)

In an eighth embodiment, the **retroviral** construct (with or without the expression of a palliative) provides a therapeutic effect by inserting itself into a virus, oncogene, or pathogenic gene, thereby inhibiting a function required for pathogenesis. This embodiment requires the direction of **retroviral** integration to a specific site in the genome by **homologous recombination**, integrase modification, or other methods (described below).

DETDESC:

DETD(248)

One technique for integrating an exogenous gene of a vector construct of a recombinant **retrovirus** into a specific site in a target cell's DNA employs **homologous recombination**. Plasmids containing sequences of DNA of greater than about 300 bp that are homologous to genomic sequences have been shown. . .

DETDESC:

DETD(249)

In order to employ **homologous recombination** in site-specific **retroviral** integration, a vector construct should be modified such that (a) homologous sequences (to the target cell's genome) are incorporated into. . . promoter. This approach has the effect of placing a region of homology near a potential free end of the double-stranded **retrovirus** vector genome. Free ends are known to increase the frequency of **homologous recombination** by a factor of approximately ten. In this approach, it may be necessary to defeat the normal mechanism of integration,. . .

US PAT NO: 5,714,381 [IMAGE AVAILABLE] L2: 5 of 67

DETDESC:

DETD(25)

Animal . . . or mutant versions of DNA encoding a human .alpha..sub.1 adrenergic receptor or homologous animal versions of these genes, by microinjection, **retroviral** infection or other means well known to those skilled in the art, into appropriate fertilized embryos in order to produce. . . transgenic animal (Hogan B. et al. Manipulating the Mouse Embryo, A Laboratory Manual, Cold Spring Harbor Laboratory (1986)) or, 2) **Homologous recombination** (Capecchi M. R. Science 244: 1288-1292 (1989); Zimmer, A. and Gruss, P. Nature 338: 150-153 (1989)) of mutant or normal,. . . transgenic animals to alter the regulation of expression or the structure .alpha.1 of these .alpha..sub.1 adrenergic receptors. The technique of **homologous recombination** is well known in the art. It replaces the native gene with the inserted gene and so is useful for. . .

US PAT NO: 5,714,313 [IMAGE AVAILABLE] L2: 6 of 67

DETDESC:

DETD(23)

The present invention further provides a vector comprising a selectable marker gene inserted into a retrotransposon, wherein the retrotransposon comprises a **retroviral** reverse transcriptase/RNase H gene domain and wherein the selectable marker gene contains an intron inserted into a coding sequence of. . . thus provides an assay for detecting inhibitors of certain retrotranspositional events. For example, inhibitors of any of the activities of **retroviral** reverse transcriptase can be detected. Additionally, inhibitors of the Ty protease or any other substituted protease, can be detected, as can inhibitors of cellular genes involved in **homologous recombination** events. Once a lead compound has been identified by the present method, its specific mode of inhibition can be determined. . . method,

however, provides an inexpensive, easy assay to screen compounds initially. Further, because of the precision with which the selected **retroviral** RT/RH can be substituted into the present vector, compounds very specific for inhibiting the selected RT/RH can be detected.

DETDESC:

DETD(27)

The His.sup.+ events obtained with HART21 and any present vector substituting different **retroviral** RT/RH domains into the retrotransposon can result, instead of from retrotransposition, from a related process termed cDNA-mediated **recombination**, a **homologous recombination** process. cDNA-mediated recombination predominates when reverse transcription products do not undergo transpositional integration catalyzed by the Tyl-encoded enzyme integrase. The cDNA product undergoes **homologous recombination** with endogenous Ty elements residing in the yeast genome. The His.sup.+ cDNA recombination events are completely dependent on functional RT/RH and, therefore, serve as a faithful biological indicator of **retroviral** RT/RH activities in yeast (FIG. 5). Additionally, a His.sup.+ event requires the RT to act as an RNA-dependent DNA polymerase. . . . the present assay to detect inhibitors of RT/RH provides a useful screen for compounds for drug intervention in therapy against **retroviral** infection.

DETDESC:

DETD(28)

That a **homologous recombination** event, rather than a retrotransposition event, occurs with any of the present **retroviral** RT/RH vectors to produce a His.sup.+ phenotype can be tested by any of several standard methods, several of which are. . . result in a significant amount of insertion of the reverse transcription product into the plasmid DNA in the cell, whereas **homologous recombination** results in insertion of the product into both the chromosome and the plasmid by virtue of the presence of Ty elements in both. Therefore, the marker on the reverse transcription product, if **homologous recombination** occurs, becomes genetically linked with markers on the plasmid, which can be readily detected by standard means.

US PAT NO: 5,712,148 [IMAGE AVAILABLE] L2: 7 of 67

DETDESC:

DETD(26)

Animal . . . of normal or mutant versions of DNA encoding a mammalian transporter or homologous animal versions of these genes, by microinjection, **retroviral** infection or other means well known to those skilled in the art, into appropriate fertilized embryos in order to produce a transgenic animal (Hogan et al., 1986) **Homologous recombination** (Cappechi, M. R., 1989; Zimmer A., and Gruss, P., 1989) of mutant or normal, human or animal versions of these. . . gene locus in transgenic animals to alter the regulation of expression or the structure of these transporters. The technique of **homologous recombination** is well known in the art. It replaces the native gene with the inserted gene and so is useful for. . .

US PAT NO: 5,705,732 [IMAGE AVAILABLE] L2: 8 of 67

DETDESC:

DETD(72)

Once cloned, the .beta..sub.2 M gene is subcloned into a plasmid based or preferentially a **retroviral**-based vector (the "gene targeting vector") such that the reading frame of the .beta..sub.2 M gene is disrupted by insertion of. . . additional selection gene (the "negative selection gene"), outside of the disrupted .beta..sub.2 m gene region which allows for selection against non-**homologous recombination**, i.e., for selection against incorporation of the entire plasmid into the genetic information of the cell rather than just the. . .

US PAT NO: 5,698,446 [IMAGE AVAILABLE] L2: 9 of 67

DETDESC:

DETD(22)

Since the various nucleotide sequences required for generating therapeutically useful **retroviral** vectors are typically harbored on more than one nucleic acid molecule and frequently contain homologous regions between the vectors, consequently, recombination may occur between the nucleotide sequences of **retroviral** gag/pol and env and other nucleic acid sequences that are conserved among the various vectors present in the packaging and/or. . . acid cassette may be inserted 3' of the homologous region in the amphotropic env expression vector CMVenvAm(Dra), so that a **homologous recombination** event will result in the production of a nucleic acid molecule containing both the 5' inhibitor/5' splice and the 3'. . .

US PAT NO: 5,691,177 [IMAGE AVAILABLE] L2: 10 of 67

SUMMARY:

BSUM(39)

Techniques for integrating a **retroviral** genome at a specific site in the DNA of a target cell involve the use of **homologous recombination**, or alternatively, the use of a modified integrase enzyme which will recognize a specific site on the target cell genome.. . .

DETDESC:

DETD(86)

In an eighth embodiment, the **retroviral** construct (with or without the expression of a palliative) provides a therapeutic effect by inserting itself into a virus, oncogene, or pathogenic gene, thereby inhibiting a function required for pathogenesis. This embodiment requires the direction of **retroviral** integration to a specific site in the genome by **homologous recombination**, integrase modification, or other methods (described below).

DETDESC:

DETD(242)

One technique for integrating an exogenous gene of a vector construct of a recombinant **retrovirus** into a specific site in a target cell's DNA employs **homologous recombination**. Plasmids containing sequences of DNA of greater than about 300 bp that are homologous to genomic sequences have been shown. . .

DETDESC:

DETD(243)

In order to employ **homologous recombination** in site-specific **retroviral** integration, a vector construct should be modified such that (a) homologous sequences (to the target cell's genome) are incorporated into. . . promoter. This approach has the effect of placing a region of homology near a potential free end of the double-stranded **retrovirus** vector genome. Free ends are known to increase the frequency of **homologous recombination** by a factor of approximately ten. In this approach, it may be necessary to defeat the normal mechanism of integration,. . .

=> d 11-20 kwic

US PAT NO: 5,686,573 [IMAGE AVAILABLE] L2: 11 of 67

DETDESC:

DETD(32)

Vectors useful for practicing the present invention include plasmids, viruses (including phage), **retroviruses**, and integrable DNA fragments (i.e., fragments integrable into the host genome by **homologous recombination**). The vector replicates and functions independently of the host genome, or may, in some instances, integrate into the genome itself.. . .

DETDESC:

DETD(38)

Cloned . . . of the present invention are useful in gene therapy, for replacing defective dopamine receptor genes in vivo. For such purposes, **retroviral** vectors as described in U.S. Pat. No. 4,650,764 to Temin and Watanabe or U.S. Pat. No. 4,861,719 to Miller may. . . be employed. Cloned genes of the present invention, or fragments thereof, may also be used in gene therapy carried out **homologous recombination** or site-directed mutagenesis. See generally Smithies et al., 1985, Nature 917: 230-234; Thomas and Capecchi, 1987, Cell 51: 503-512; Bertling,. . .

US PAT NO: 5,683,912 [IMAGE AVAILABLE] L2: 12 of 67

DETDESC:

DETD(58)

The transfer of nucleic acid material into mammalian hosts for the purpose of generating transgenic animals can be accomplished by

microinjection, **retroviral** infection or other means well known to those skilled in the art, of the material into appropriate fertilized embryos. (See, for example, Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual (Cold Spring Harbor Laboratory, 1986). **Homologous recombination** can also be used for the generation of transgenic animals according to the present invention. **Homologous recombination** techniques are well known in the art. **Homologous recombination** replaces a native (endogenous) gene with a recombinant or mutated gene to produce an animal that cannot express a native (endogenous) alpha9 receptor subunit but can express, for example, a mutated receptor subunit. In contrast to **homologous recombination**, microinjection adds genes to the host genome, without removing host genes. Microinjection can produce a transgenic animal that is capable. . .

US PAT NO: 5,681,746 [IMAGE AVAILABLE] L2: 13 of 67

DETDESC:

DETD(42)

An . . . packaging cell lines useful in the invention is the production therefrom of replication incompetent virions, or avoidance of generating replication-competent **retrovirus** (RCR) [Munchau et al., Virology, vol. 176:262-65, 1990]. This will ensure that infectious **retroviral** particles harboring the recombinant retrovital vectors of the invention will be incapable of independent replication in target cells, be they. . . the possibility of insertional mutagenesis and its associated problems. RCR production can occur in at least two ways: (1) through **homologous recombination** between the therapeutic proviral DNA and the DNA encoding the **retroviral** structural genes ("gag/pol" and "env") present in the packaging cell line; and (2) generation of replication-competent virus by **homologous recombination** of the proviral DNA with the very large number of defective endogenous proviruses found in the packaging cell line.

DETDESC:

DETD(61)

In . . . leads to integration of the viral genome into a chromosome of the recipient cell, as occurs in the case of **retroviral** infection, **homologous recombination** or use of a modified integrase enzyme which directs insertion to a specific site can be utilized. Such site-specific insertion. . .

US PAT NO: 5,677,139 [IMAGE AVAILABLE] L2: 14 of 67

SUMMARY:

BSUM(43)

Many . . . include vital vectors, episomal plasmid vectors, stably integrating plasmid vectors, and artificial chromosome vectors. Vital vectors include those derived from **retroviruses**, adenoviruses, adeno-associated viruses, herpesviruses, and pox viruses. Vital vectors may be delivered as virus particles or by another delivery mechanism. . . including synthetic nucleic acids. Vectors may be designed to integrate at a specific location in the genome by insertion or **homologous recombination**, may integrate randomly or may remain in

the nucleus as a stable episomal nucleic acid. All of the above vectors. . .

US PAT NO: 5,675,063 [IMAGE AVAILABLE] L2: 15 of 67

SUMMARY:

BSUM(26)

DNA can be introduced into embryonic stem (ES) cells by transfection, **retroviral** infection, or electroporation. The most important advantage for gene transfer into animals is that cells carrying the transgene can be selected for before being injected into a blastocyst. For example, ES cells were infected with **retroviral** vectors, or transfected with plasmids, carrying the neo gene. This gene confers resistance to the antibiotic G418. Only ES cells. . . F2 generation were G418-resistant. Because ES cells can be manipulated in vitro before injection into the embryo, geneticists can use **homologous recombination** to produce transgenic animals with mutations, specific genes or to replace a mutant gene with the normal equivalent.

US PAT NO: 5,665,585 [IMAGE AVAILABLE] L2: 16 of 67

DETDESC:

DETD(37)

In . . . or, in a most preferred embodiment, be assisted by transformation with a vector inserting it into the host chromosome by **homologous recombination**, for example, with **retroviral** vectors, transposons or other DNA elements which promote integration of DNA sequences in chromosomes. A vector is employed which is. . . T. reesei, such vectors may provide a gene encoded by T. reesei, such as the cellobiohydrolase I gene, to promote **homologous recombination** at a specific site on the host chromosome.

US PAT NO: 5,658,786 [IMAGE AVAILABLE] L2: 17 of 67

DETDESC:

DETD(26)

Animal . . . of normal or mutant versions of DNA encoding a mammalian transporter or homologous animal versions of these genes, by microinjection, **retroviral** infection or other means well known to those skilled in the art, into appropriate fertilized embryos in order to produce a transgenic animal (24) or 2) **Homologous recombination** (7,82) of mutant or normal, human or animal versions of these genes with the native gene locus in transgenic animals to alter the regulation of expression or the structure of these transporters. The technique of **homologous recombination** is well known in the art. It replaces the native gene with the inserted gene and so is useful for. . .

US PAT NO: 5,658,783 [IMAGE AVAILABLE] L2: 18 of 67

DETDESC:

DETD(8)

Vectors useful for practicing the present invention include plasmids,

viruses (including phage), **retroviruses**, and integratable DNA fragments (i.e., fragments integratable into the host genome by **homologous recombination**). The vector replicates and functions independently of the host genome, or may, in some instances, integrate into the genome itself.. . .

US PAT NO: 5,658,782 [IMAGE AVAILABLE] L2: 19 of 67

DETDESC:

DETD(11)

Vectors useful for practicing the present invention include plasmids, viruses (including phage), **retroviruses**, and integratable DNA fragments (i.e., fragments integratable into the host genome by **homologous recombination**). The vector replicates and functions independently of the host genome, or may, in some instances, integrate into the genome itself.. . .

US PAT NO: 5,656,465 [IMAGE AVAILABLE] L2: 20 of 67

DETDESC:

DETD(27)

Recombinant fowlpox viruses (FPV) were constructed by **homologous recombination** in a manner analogous to that previously described (Jenkins, et al. AIDS Research and Human **Retroviruses** 7:991-998 (1991). Foreign sequences were inserted at the Bg/II site in the BamHI J region of the FPV genome. FPV. . .

=> d 2,3,4 bib ab

US PAT NO: 5,716,832 [IMAGE AVAILABLE] L2: 2 of 67
DATE ISSUED: Feb. 10, 1998
TITLE: Packaging cells
INVENTOR: Jack R. Barber, San Diego, CA
Douglas J. Jolly, La Jolla, CA
James G. Respess, San Diego, CA
Stephen M. W. Chang, San Diego, CA
ASSIGNEE: Chiron Viagene, Inc. (U.S. corp.)
APPL-NO: 08/462,492
DATE FILED: Jun. 5, 1995
ART-UNIT: 185
PRIM-EXMR: Mindy Fleisher
ASST-EXMR: Robert Schwartzman
LEGAL-REP: Norman J. Kruse, Robert P. Blackburn

US PAT NO: 5,716,832 [IMAGE AVAILABLE] L2: 2 of 67

ABSTRACT:
The invention described herein allows the production of recombinant retroviruses (retroviral vector particles) from producer cells which are safer and of higher titre than normal. In addition, methods are provided for making helper cells which, when a recombinant retrovirus genome is introduced to make a producer line, produce particles that are targeted toward particular cell types. Methods are also provided for making recombinant retrovirus systems adapted to infect a particular cell type,

such as a tumor, by binding the retrovirus or recombinant retrovirus in the particular cell type. Methods are also provided for producing recombinant retroviruses which integrate in a specific small number of places in the host genome, and for producing recombinant retroviruses from transgenic animals.

US PAT NO: 5,716,826 [IMAGE AVAILABLE] L2: 3 of 67
DATE ISSUED: Feb. 10, 1998
TITLE: Recombinant retroviruses
INVENTOR: Harry E. Gruber, Rancho Santa Fe, CA
Douglas J. Jolly, Leucadia, CA
James G. Respess, San Diego, CA
Paul K. Laikind, San Diego, CA
ASSIGNEE: Chiron Viagene, Inc. (U.S. corp.)
APPL-NO: 08/136,739
DATE FILED: Oct. 12, 1993
ART-UNIT: 185
PRIM-EXMR: George G. Elliott
ASST-EXMR: Robert Schwartzman
LEGAL-REP: Norman J.Seed & Berry Kruse, Robert P. Blackburn

US PAT NO: 5,716,826 [IMAGE AVAILABLE] L2: 3 of 67

ABSTRACT:
Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

US PAT NO: 5,716,613 [IMAGE AVAILABLE] L2: 4 of 67
DATE ISSUED: Feb. 10, 1998
TITLE: Recombinant retroviruses
INVENTOR: Harry E. Guber, San Diego, CA
Douglas J. Jolly, La Jolla, CA
James G. Respess, San Diego, CA
Paul K. Laikind, San Diego, CA
ASSIGNEE: Chiron Viagene, Inc. (U.S. corp.)
APPL-NO: 08/474,736
DATE FILED: Jun. 7, 1995
ART-UNIT: 185
PRIM-EXMR: George G. Elliott
ASST-EXMR: Robert Schwartzman
LEGAL-REP: Norman J.Seed & Berry Kruse, Robert P. Blackburn

US PAT NO: 5,716,613 [IMAGE AVAILABLE] L2: 4 of 67

ABSTRACT:
Recombinant retroviruses carrying a vector construct capable of preventing, inhibiting, stabilizing or reversing infectious, cancerous or auto-immune diseases are disclosed. More specifically, the recombinant

retroviruses of the present invention are useful for (a) stimulating a specific immune response to an antigen or a pathogenic antigen; (b) inhibiting a function of a pathogenic agent, such as a virus; and (c) inhibiting the interaction of an agent with a host cell receptor. In addition, eucaryotic cells infected with, and pharmaceutical compositions containing such a recombinant retrovirus are disclosed. Various methods for producing recombinant retroviruses having unique characteristics, and methods for producing transgenic packaging animals or insects are also disclosed.

=> d 2 clms

US PAT NO: 5,716,832 [IMAGE AVAILABLE] L2: 2 of 67

CLAIMS:

CLMS(1)

We claim:

1. A method of producing a recombinant retrovirus, comprising growing a producer cell having a genome comprising:
(a) a gene of interest and a packaging signal of a first retrovirus;
(b) gag and pol genes of the first retrovirus, absent a packaging signal;
(c) a hybrid env gone absent a packaging signal, the product of said hybrid env gone comprising a cytoplasmic segment of the first retrovirus, and a binding segment exogenous to the first retrovirus.

CLMS(2)

2. A xenotropic packaging cell line which, upon introduction of a vector construct, produces viral particles uncontaminated by replication competent virus.

CLMS(3)

3. The packaging cell line of claim 2 wherein the cell line produces at least equal vector titre as compared to a standard mouse amphotropic packaging cell line PA 317 when HT1080 cells are infected.

CLMS(4)

4. A polytropic packaging cell line which, upon introduction of a vector construct, produces vital particles uncontaminated by replication competent virus.

CLMS(5)

5. The packaging cell line of claim 4 wherein the packaging cell line, upon introduction of a vector construct, produces at least a ten-fold increase in vector titre as compared to a standard measure amphotropic packaging cell line PA 317 when 293 cells are infected.

CLMS(6)

6. A polytropic packaging cell line wherein the packaging cell line, upon introduction of a vector construct, produces viral particles which infect cells of kidney lineage, but not cells or fibreblast, epithelial,

T-cell or monocyte lineage.

CLMS(7)

7. A non-mouse packaging cell the carrying on separate operons the genes for gag/pol and env, said operons lacking retroviral LTR sequences and which, upon introduction of an N2 type vector construct, produces no helper virus after at least twenty days passage in culture.

CLMS(8)

8. The cell line of claim 7 wherein the cell line is an amphotropic packaging cell line.

CLMS(9)

9. The cell line of claim 7 wherein the cell line is a polytropic packaging cell line.

CLMS(10)

10. The cell line of claim 7 wherein the cell line is a xenotropic packaging cell line.

CLMS(11)

11. A method of producing a recombinant retrovirus, comprising:
(a) introducing packaging genes from a retroviral vector system into a cell line, said cell line having no endogenous proviruses which produce transcripts packageable by the retroviral vector system;
(b) selecting for cells that produce at least a ten-fold increase in viral packaging protein as compared to a standard mouse amphotropic packaging cell line PA317, and that, upon introduction of a vector construct, produce at least a ten-fold increase in vector titre as compared to a standard mouse amphotropic packaging cell line PA317; and
(c) growing the cells selected in step (b) such that recombinant retrovirus is produced.

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E4            3      GUNZBURGER D/AU
E5            5      GUNZBURGER L/AU
E6           14      GUNZBURGER L K/AU
E7            3      GUNZCLER P/AU
E8            1      GUNZE C M B/AU
E9            1      GUNZEL/AU
E10           1      GUNZEL A/AU
E11          13      GUNZEL A R/AU
E12           6      GUNZEL APEL A R/AU
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=> s e3

L1          38 "GUNZBURG W H"/AU

=> e saller r m/au

E1           1     SALLER L/AU
E2          68     SALLER R/AU
E3           9 --> SALLER R M/AU
E4           2     SALLER S/AU
E5           7     SALLER U/AU
E6           2     SALLER Y/AU
E7           1     SALLERA SANMARTI L/AU
E8           2     SALLERAS J M/AU
E9           8     SALLERAS J P/AU
E10        114     SALLERAS L/AU
E11          2     SALLERAS L I/AU
E12          2     SALLERAS L Y/AU

=> s e3

L2           9 "SALLER R M"/AU

=>  s l1 and l2

L3           3 L1 AND L2

=> d 1-3 bib ab


L3   ANSWER 1 OF 3  MEDLINE
AN   1998105826     MEDLINE
DN   98105826
TI   Construction and characterization of a hybrid mouse mammary tumor
     virus/murine leukemia virus-based retroviral vector.
AU   Saller R M; Ozturk F; Salmons B; Gunzburg W H
CS   Institut fur Molekulare Virologie, GSF-Forschungszentrum fur Umwelt
     und Gesundheit, Oberschleissheim, Germany.
SO   JOURNAL OF VIROLOGY, (1998 Feb) 72 (2) 1699-703.
     Journal code: KCV. ISSN: 0022-538X.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   Priority Journals; Cancer Journals
EM   199804
EW   19980403
AB   Mouse mammary tumor virus (MMTV)-based vectors are characterized by
     low titers. In an effort to transfer MMTV-specific regulation of
     gene expression to a more efficient murine leukemia virus (MLV)
     vector, we have replaced the complete 3' U3 region of MLV with the
     complete U3 region of MMTV. Virus titers were not significantly
     affected by this modification, there was no impairment of reverse
     transcription and integration, and after infection of cells, the
     MMTV promoter is duplicated and translocated to the 5' long terminal
     repeat, resulting in glucocorticoid-regulatable RNA expression.

L3   ANSWER 2 OF 3  MEDLINE
AN   96022220     MEDLINE
DN   96022220
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TI Construction of retroviral vectors for targeted delivery and expression of therapeutic genes.
AU Salmons B; **Saller R M**; Baumann J G; **Gunzburg W H**
CS Bavarian Nordic Research Institute, Oberschleissheim, Germany..
SO LEUKEMIA, (1995 Oct) 9 Suppl 1 S53-60. Ref: 44
Journal code: LEU. ISSN: 0887-6924.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals; Cancer Journals
EM 199602
AB Current gene therapy protocols take an ex vivo approach in which cells are removed from a patient, genetically modified and then reimplanted. However this kind of approach is both cumbersome and costly, requiring high tech facilities and is limited to cell types that can be easily cultured. The in vivo delivery of genes by retroviral vectors will greatly facilitate gene therapy protocols of the future. However before in vivo gene therapy becomes a reality a number of problems must be overcome. Ideally therapeutic genes should be delivered only to the relevant cell type and/or expressed in this cell type. Strategies are described that (I) limit therapeutic gene delivery, using pseudotyping or vectors based on retroviruses that show a restricted infection spectrum or (II) limit the expression of transferred genes by inclusion of tissue specific promoters or cis acting regulatory elements. The combination of some of these strategies should permit the construction of novel retroviral vectors that provide safe and targeted in vivo gene transfer.

L3 ANSWER 3 OF 3 MEDLINE
AN 95344681 MEDLINE
DN 95344681
TI Retroviral vectors directed to predefined cell types for gene therapy.
AU **Gunzburg W H**; **Saller R M**; Salmons B
CS GSF-Forschungszentrum fur Unwelt und Gesundheit GmbH, Institut fur Molekulare Virologie, Oberschleissheim, Germany..
SO BIOLOGICALS, (1995 Mar) 23 (1) 5-12. Ref: 41
Journal code: AMW. ISSN: 1045-1056.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199511

=> s (homolog? (3a) recomb?) and retrovir?

L4 167 (HOMOLOG? (3A) RECOMB?) AND RETROVIR?

=> s homologous recombination and retrovir?

L5 132 HOMOLOGOUS RECOMBINATION AND RETROVIR?

=> s l5 range=,1995

L6 101 L5

=> s l5 range=,1994

L7 89 L5

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=> d 1-10 bib ab

L8 ANSWER 1 OF 53 MEDLINE DUPLICATE 1
AN 94187082 MEDLINE
DN 94187082
TI **Retrovirus** recombination depends on the length of sequence identity and is not error prone.
AU Zhang J; Temin H M
CS McArdle Laboratory for Cancer Research, University of Wisconsin-Madison 53706.
NC CA-22443 (NCI)
CA-07175 (NCI)
SO JOURNAL OF VIROLOGY, (1994 Apr) 68 (4) 2409-14.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199406
AB **Retroviruses**, as a result of the presence of two identical genomic RNA molecules in their virions, recombine at a high rate. When nonhomologous RNA is present in the dimer RNA molecules, nonhomologous recombination can occur, although the rate is very low, only 0.1% of the rate of essentially **homologous recombination** (J. Zhang and H. M. Temin, Science 259:234-238, 1993). We found, as is found in naturally occurring highly oncogenic **retroviruses** (J. Zhang and H. M. Temin, J. Virol. 67:1747-1751, 1993), that the crossovers usually occur at a short region of sequence identity. We modified the previously studied vectors to study the effect of different lengths of short regions of sequence identity in the midst of otherwise nonidentical sequences. We found that the efficiency of recombination depends on the length of this sequence identity. However, the highest rate in such molecules remained lower than for recombination between essentially homologous molecules, even when there was extensive sequence identity. Junction sequences of the recombinants indicated that **retrovirus** recombination is not an error-prone process as was reported for human immunodeficiency virus reverse transcriptase by using a cell-free system (J. A. Peliska and S. J. Benkovic, Science 258:1112-1118, 1992).

L8 ANSWER 2 OF 53 MEDLINE
AN 94331440 MEDLINE
DN 94331440
TI Characterization of a replication-competent **retrovirus** resulting from recombination of packaging and vector sequences.

AU Otto E; Jones-Trower A; Vanin E F; Stambaugh K; Mueller S N; Anderson W F; McGarrity G J
CS Genetic Therapy Inc., Gaithersburg, MD 20878.
SO HUMAN GENE THERAPY, (1994 May) 5 (5) 567-75.
Journal code: A12. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411
AB A replication-competent **retrovirus** (RCR) was detected by S+/L- assays in three lots of **retroviral** vector G1Na that were harvested on consecutive days from a single culture of PA317/G1Na producer cells. Using a number of **retrovirus** -specific primer pairs, it was shown that this RCR was a novel recombinant created by exchanges between G1Na and helper sequence pPAM3 and was not an existing RCR introduced by cross-contamination. Sequencing of clones of DNA amplified in six independent PCR reactions confirmed that the 3' portion of this RCR was composed of **retroviral** envelope sequences unique to pPAM3 joined to a 3' long terminal repeat (LTR) unique to G1Na. Comparison of pPAM3 and G1Na sequences at the site corresponding to this junction revealed a short segment of patchy nucleotide identity (8 out of 10 bp), suggesting that these helper and vector sequences were joined by **homologous recombination**. Generation of RCR by exchanges between helper and vector sequences underscores the necessity of testing by efficient methods all **retroviral** vectors for the presence of RCR before their use. Production of 171 lots (855 liters) of various **retroviral** vectors that were free of RCR, including 42 lots of G1Na, however, indicates that the combination of exchanges required to generate an RCR are infrequent in this system.

L8 ANSWER 3 OF 53 MEDLINE DUPLICATE 2
AN 94076409 MEDLINE
DN 94076409
TI One **retroviral** RNA is sufficient for synthesis of viral DNA.
AU Jones J S; Allan R W; Temin H M
CS McArdle Laboratory for Cancer Research, University of Wisconsin, Madison 53706.
NC CA22443 (NCI)
CA07175 (NCI)
NCI CA09075 (NCI)
SO JOURNAL OF VIROLOGY, (1994 Jan) 68 (1) 207-16.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199403
AB We used previously characterized spleen necrosis virus-based **retroviral** vectors and helper cells to study the strand transfers that occur during the reverse-transcription phase of a single cycle of **retroviral** replication. The conditions used selected only for formation of an active provirus rather than for expression of multiple drug resistance markers. In nonrecombinant proviruses the minus- and plus-strand DNA primer transfers were almost completely intramolecular. However, as previously reported, recombinant proviruses contained approximately

equal proportions of inter- and intramolecular minus-strand DNA primer transfers. Thus, we conclude that in the absence of recombination, one molecule of **retroviral** RNA is sufficient for viral DNA synthesis. Large deletions and deletions with insertions were detected primarily at a limited number of positions which appear to be hot spots for such events, the primer binding site and regions containing multiple inverted repeats. At these hot spots, the rate of deletions and deletions with insertions visible with PCR was about 10% per genome per replication cycle. Other deletions and deletions with insertions (detectable with PCR) occurred at a rate of about 0.5%/kb per replication cycle. Crossovers occurred at a rate of about 6%/kb per replication cycle under single-selection conditions. This rate is comparable to the rate that we reported previously under double-selection conditions, indicating that **retroviral homologous recombination** is not highly error prone. The combined rates of deletions and deletions with insertions at hot spots (10% per genome per replication cycle) and other sites (0.5%/kb per replication cycle) and the rate of crossovers (6%/kb per replication cycle) indicate that on average, full-size (10-kb) type C **retroviruses** undergo an additional or aberrant strand transfer about once per cycle of infection.

L8 ANSWER 4 OF 53 MEDLINE
AN 94082449 MEDLINE
DN 94082449
TI Pathogenicity of a subgroup C feline leukemia virus (FeLV) is augmented when administered in association with certain FeLV recombinants.
AU Mathes L E; Pandey R; Chakrabarti R; Hofman F M; Hayes K A; Stromberg P; Roy-Burman P
CS Center for Retrovirus Research, Ohio State University, Columbus 43210.
NC CA51485 (NCI)
T32-CA09320 (NCI)
SO VIROLOGY, (1994 Jan) 198 (1) 185-95.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199403
AB There is evidence to suggest that infectious feline leukemia viruses (FeLVs) may be altered biologically because of **homologous recombination** with non-infectious endogenous FeLV (enFeLV) sequences in the infected cells. To evaluate the role of such recombination events in FeLV pathogenesis, a molecular clone of subgroup C FeLV, Sarma strain (FSC), was tested for induction of aplastic anemia in the absence or presence of mixtures of recombinants between FSC and an enFeLV element. In the recombinants, FSC sequences in the viral surface glycoprotein (SU) protein were variably replaced by the corresponding sequences of the enFeLV. The results showed that the virus mixtures varied in their infectivity to neonatal specific pathogen-free cats. One group of mixtures, although exhibiting relatively reduced infectivity, represented the most acute disease-inducing agents. The presence of recombinants in this mixture significantly accelerated the development of erythrocyte aplasia compared to cats infected with FSC alone. In addition, infected cells appeared to be distributed differently in various hematopoietic organs with respect to infection with FSC

versus viral mixture. Viral recombinants which were present in this inoculum mixture, however, could not be detected in the plasma or infected tissues of the cats at the end stage of the disease, although their presence in the plasma at the early stages could be detected. Clearly, parental FSC outgrew the recombinants in the infected animals, since its detection was prominent at all stages of the progression of the disease. Therefore, we hypothesize that recombinants initially present in the infected animals, while only poorly replicated compared to FSC in the host, might have had the opportunity to infect certain target cells (potentially erythroid progenitor cells) and then disappeared with the associated cytopathic effect.

L8 ANSWER 5 OF 53 BIOSIS COPYRIGHT 1998 BIOSIS
AN 94:482569 BIOSIS
DN 97495569
TI Versatile **retroviral** vectors for potential use in gene therapy.
AU Hawley R G; Lieu F H L; Fong A Z C; Hawley T S
CS Div. Cancer Res., Reichmann Res. Build., S218, Sunnybrook Health Sci. Cent., 2075 Bayview Ave., Toronto, ON M4N 3M5, CAN
SO Gene Therapy 1 (2). 1994. 136-138.
LA English
AB A set of **retroviral** vectors is described whose capacity for high efficiency transduction of functional genes into undifferentiated murine embryonic and haematopoietic cells makes them ideally suited for preclinical studies with murine models. Multiple unique cloning sites permit insertion of genes into the vectors such that no selectable marker exists or either the neomycin phosphotransferase (neo) gene, the hygromycin B phosphotransferase (hph) gene or the puromycin N-acetyl transferase (pac) gene is included as a dominantly acting selectable marker. Because the sequences in the viral gag region shown to improve the encapsidation of viral RNA have been modified to prevent viral protein synthesis and all env sequences have been removed to eliminate helper virus production by **homologous recombination** with packaging DNA, these vectors might prove useful in human gene therapy protocols.

L8 ANSWER 6 OF 53 MEDLINE
AN 94265646 MEDLINE
DN 94265646
TI [Transgenic mice--biological fundamentals, practices and applications].
Transgene Mause--Biologische Grundlagen, Praktiken und Anwendung.
AU Balling R
CS Institut fur Saugetiergenetik, GSF-Forschungszentrum fur Umwelt und Gesundheit, Oberschleissheim..
SO DTW. DEUTSCHE TIERARZTLICHE WOCHENSCHRIFT, (1994 Mar) 101 (3) 94-5. Ref: 10
Journal code: ECT. ISSN: 0341-6593.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA German
EM 199409
AB The transfer of genes into the germline of mice has become a standard technique of modern biomedical research. In addition to direct microinjection of DNA into the pronuclei of fertilized mouse

eggs, genes can now also be inactivated via **homologous recombination** in embryonic stem cells (gene targeting). In the future it will be possible to inactivate any cloned gene via **homologous recombination** in ES-cells and establish corresponding mouse mutants.

L8 ANSWER 7 OF 53 BIOSIS COPYRIGHT 1998 BIOSIS
AN 93:585044 BIOSIS
DN 97004414
TI High rate of genetic rearrangement during replication of a Moloney murine leukemia virus-based vector.
AU Varela-Echavarria A; Proprock C M; Ron Y; Dougherty J P
CS Dep. Mol. Genetics Microbiol., Robert Wood Johnson Med. Sch., University Medicine, Dentistry New Jersey, 675 Hoes Lane, Piscataway, NJ 08854-5635, USA
SO Journal of Virology 67 (11). 1993. 6357-6364. ISSN: 0022-538X
LA English
AB A protocol was designed to measure the forward mutation rate over an entire gene replicated as part of a Moloney murine leukemia virus-based vector. For these studies, the herpes simplex virus thymidine kinase (tk) gene under the control of the spleen necrosis virus U3 promoter was used as target sequence since it allows selection for either the functional or the inactivated gene. Our results indicate that after one round of **retroviral** replication, the tk gene is inactivated at an average rate of 0.08 per cycle of replication. Southern blotting revealed that the majority of the mutant proviruses resulted from gross rearrangements and that deletions of spleen necrosis virus and tk sequences were the most frequent cause of the gene inactivation. Sequence analysis of the mutant proviruses suggested that homologous as well as nonhomologous recombination was involved in the observed rearrangements. Some mutations consisted of simple deletions, and others consisted of deletions combined with insertions. The frequency at which these mutations occurred during one cycle of **retroviral** replication provides evidence indicating that Moloney murine leukemia virus-based vectors may undergo genetic rearrangement at high rates. The high rate of rearrangement and its relevance for **retrovirus**-mediated gene transfer are discussed.

L8 ANSWER 8 OF 53 MEDLINE DUPLICATE 3
AN 93267761 MEDLINE
DN 93267761
TI Alteration of location of dimer linkage sequence in **retroviral** RNA: little effect on replication or **homologous recombination**.
AU Jones J S; Allan R W; Temin H M
CS McArdle Laboratory for Cancer Research, University of Wisconsin, Madison 53706.
NC CA22443 (NCI)
CA07175 (NCI)
CA09075 (NCI)
SO JOURNAL OF VIROLOGY, (1993 Jun) 67 (6) 3151-8.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199308
AB **Retrovirus** particles contain a dimer of **retroviral**

genomic RNA. A defined region of the **retrovirus** genome has previously been shown to be important for both dimerization and encapsidation. To study the importance of the position of this encapsidation and dimerization signal for **retroviral** replication and **homologous recombination**, we used a previously described spleen necrosis virus-based helper cell system. This system allows **retroviral** vectors with multiple genetic markers to be studied after a single cycle of **retroviral** replication. The sequence responsible for dimerization, the encapsidation/dimer linkage sequence (E/DLS), was moved from its normal location near the 5' end of the **retroviral** genome to a location near the 3' end of the genome. We characterized four pairs of **retroviral** vectors: (i) with both E/DLSs at the 5' ends of the genomes, (ii) with both E/DLSs at the 3' ends of the genomes, and (iii) two with one E/DLS at the 5' end of the genome and one at the 3' end of the genome. We found that moving the E/DLS to the 3' end of the genome resulted in at most an approximately factor of 5 reduction in virus titer in a single cycle of **retroviral** replication. Furthermore, we found no changes that were attributable to the alteration of the position of the E/DLS in the minus-strand DNA primer transfers or the plus-strand DNA primer transfers, the rate of **homologous recombination**, or the number of internal template switches in recombinant proviruses. These results indicate that any alignment or conformation necessary for **retroviral** replication or recombination is not the result of the position of the E/DLS.

L8 ANSWER 9 OF 53 MEDLINE DUPLICATE 4
AN 93390966 MEDLINE
DN 93390966
TI Long cellular repeats flanking a defective HTLV-I provirus: implication for site-targeted integration.
AU Kubota S; Furuta R; Maki M; Siomi H; Hatanaka M
CS Institute for Virus Research, Kyoto University, Japan..
SO ONCOGENE, (1993 Oct) 8 (10) 2873-7.
Journal code: ONC. ISSN: 0950-9232.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199312
AB **Retroviruses** generally integrate as proviruses which are flanked by long-terminal repeats (LTRs) on both 5' and 3' ends. Since these LTRs are required for the efficient integration mediated by the viral integrase, it is believed that defective proviruses with a single LTR are normally formed by deletion after integration. However, we found no deletion of cellular sequences around the integration site of such a defective HTLV-1. Rather, we identified 99 bp-long direct repeats adjacent to both ends of the defective provirus. The repeated cellular sequences contained a potential poly(A) signal followed by a **retroviral** primer-binding-site-like sequence. The presence of the direct repeats of cellular sequences can be explained by the integration of the defective virus through **homologous recombination** between cellular and viral read-through sequences.

L8 ANSWER 10 OF 53 MEDLINE DUPLICATE 5
AN 93345780 MEDLINE
DN 93345780

TI Synthetic retrotransposon vectors for gene therapy.
AU Chakraborty A K; Zink M A; Boman B M; Hodgson C P
CS Creighton Cancer Center/Dept. of Biomedical Sciences, Creighton School of Medicine, Omaha, Nebraska 68178..
NC 1R29GM41314-4 (NIGMS)
SO FASEB JOURNAL, (1993 Jul) 7 (10) 971-7.
Journal code: FAS. ISSN: 0892-6638.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199311
AB New gene therapy methods are rapidly being developed to permit the expression of tumor suppressor genes, cytotoxins, anticancer antigens, and immunoregulatory proteins in the treatment of cancer. Large-scale testing in humans has been delayed by questions concerning the safety and effectiveness of preferred **retroviral** vectors and helper cells. These vector systems are limited by their ability to undergo **homologous recombination** with endogenous **retroviruses** or helper-viral sequences, resulting in release of replication-competent **retrovirus** (RCR). In addition, transcriptional inactivation of the **retroviral** promoter often occurs, caused in part by methylation of CpG islands in the **retroviral** long terminal repeats (LTRs). We report the production of highly specific retrovectors using gene amplification together with oligonucleotide building blocks. The synthetic vectors were based on mouse VL30 retrotransposon NVL3, and lacked homology to **retroviral** helper gene sequences. Three of four constructs made by gene amplification yielded biologically active vectors. These constructs efficiently transmitted and stably inserted a neomycin resistance marker gene into the genome of recipient cells, expressing an abundant RNA species of the expected size in the absence of detectable replication competent **retrovirus**. The vectors and techniques described enable widely applicable expression modes using generic helper cells, and require only approximately 1.3 kb of cis-acting vector RNA sequences for faithful transfer and expression of genetic material.

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FILE 'MEDLINE, BIOSIS' ENTERED AT 13:17:34 ON 12 MAR 1998
E GUNZBURG W H/AU
L1 38 S E3
E SALLER R M/AU
L2 9 S E3
L3 3 S L1 AND L2
L4 167 S (HOMOLOG? (3A) RECOMB?) AND RETROVIR?
L5 132 S HOMOLOGOUS RECOMBINATION AND RETROVIR?
L6 101 S L5
L7 89 S L5
L8 53 DUPLICATE REMOVE L7 (36 DUPLICATES REMOVED)

=> s l5 and (host or chromosom?)

L9 36 L5 AND (HOST OR CHROMOSOM?)

=> d 1-10 bib ab

L9 ANSWER 1 OF 36 MEDLINE
AN 1998105778 MEDLINE
DN 98105778
TI The application of a **homologous recombination** assay revealed amino acid residues in an LTR-retrotransposon that were critical for integration.
AU Atwood A; Choi J; Levin H L
CS Laboratory of Eukaryotic Gene Regulation, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO JOURNAL OF VIROLOGY, (1998 Feb) 72 (2) 1324-33.
Journal code: KCV. ISSN: 0022-538X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199804
EW 19980403
AB **Retroviruses** and their relatives, the LTR-retrotransposons, possess an integrase protein (IN) that is required for the insertion of reverse transcripts into the genome of **host** cells. Schizosaccharomyces pombe is the **host** of Tf1, an LTR-retrotransposon with integration activity that can be studied by using techniques of yeast genetics. In this study, we sought to identify amino acid substitutions in Tf1 that specifically affected the integration step of transposition. In addition to seeking amino acid substitutions in IN, we also explored the possibility that other Tf1 proteins contributed to integration. By comparing the results of genetic assays that monitored both transposition and reverse transcription, we were able to seek point mutations throughout Tf1 that blocked transposition but not the synthesis of reverse transcripts. These mutant versions of Tf1 were candidates of elements that possessed defects in the integration step of transposition. Five mutations in Tf1 that resulted in low levels of integration were found to be located in the IN protein: two substitutions in the N-terminal Zn domain, two in the catalytic core, and one in the C-terminal domain. These results suggested that each of the three IN domains was required for Tf1 transposition. The potential role of these five amino acid residues in the function of IN is discussed. Two of the mutations that reduced integration mapped to the RNase H (RH) domain of Tf1 reverse transcriptase. The Tf1 elements with the RH mutations produced high levels of reverse transcripts, as determined by recombination and DNA blot analysis. These results indicated that the RH of Tf1 possesses a function critical for transposition that is independent of the accumulation of reverse transcripts.

L9 ANSWER 2 OF 36 MEDLINE
AN 95336307 MEDLINE
DN 95336307
TI LTR-directed **homologous recombination** of full-length HIV-1 provirus clone in recA(-) bacteria.
AU Yamada K; Morozumi H; Okamoto T
CS Department of Molecular Genetics, Nagoya City University Medical School, Aichi, Japan.
SO ARCHIVES OF VIROLOGY, (1995) 140 (6) 1007-14.
Journal code: 8L7. ISSN: 0304-8608.

CY Austria
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199510
AB During molecular cloning of full-length **retroviral** plasmid clones occurrence of **homologous recombination** (HR) between LTR regions is frequently observed. In order to evaluate appropriate **host** bacterial strains for cloning such HR-prone plasmids, we utilized a linearized template plasmid containing a full-length HIV-1 proviral sequence. The plasmid was linearized within the viral sequence so that plasmid transformed bacteria would grow only when the plasmid was circularized by HR. Using this genetic system for detecting HR, we evaluated the frequency of HR in various recA(-) bacterial strains which are commercially available and in some recA-null strains in which recA-defective phenotype was constructed by P1 transduction. We found that HR occurred even in recA-null strains although in lesser frequencies. The nucleotide sequence analysis at the junction of recombination revealed no loss, insertion or duplication of DNA sequence. It is suggested that recombination machinery other than the RecA system is involved.

L9 ANSWER 3 OF 36 MEDLINE
AN 95211017 MEDLINE
DN 95211017
TI Activities of granulocyte-macrophage colony-stimulating factor revealed by gene transfer and gene knockout studies.
AU Dranoff G; Mulligan R C
CS Dana-Farber Cancer Institute, Boston, Massachusetts.
SO STEM CELLS, (1994) 12 Suppl 1 173-82; discussion 182-4. Ref: 65
Journal code: BN2. ISSN: 1066-5099.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199507
AB We used **retroviral** mediated gene transfer and gene knockout technologies to explore the in vivo functions of murine granulocyte-macrophage colony-stimulating factor (GM-CSF) [1, 2]. In tumor vaccination experiments, GM-CSF was the most potent molecule of a large number of cytokines, adhesion molecules and other immunomodulators for the induction of specific and long-lasting anti-tumor immunity. Vaccination required activities of both CD4 and CD8 positive lymphocytes, and likely involved the augmentation by GM-CSF of **host** professional antigen-presenting cell function. Mice engineered by **homologous recombination** techniques in embryonic stem cells to lack GM-CSF demonstrated no significant perturbations in steady-state hematopoiesis. All mutant animals, however, developed the accumulation of surfactant proteins and lipids in the alveolar space, the defining feature of the idiopathic human disorder pulmonary alveolar proteinosis. Surfactant lipid and protein content were increased in the absence of alterations in surfactant protein mRNA, supporting the concept that surfactant clearance or catabolism was perturbed. Extensive lymphoid hyperplasia associated with lung airways and blood vessels was also found, yet no infectious agents could be isolated. These results demonstrate that GM-CSF is not an

essential growth factor for basal hematopoiesis and reveal an unexpected, critical role for GM-CSF in pulmonary homeostasis. It is tempting to speculate that the ability of GM-CSF to modulate the uptake and processing of particulate material underlies the mechanisms of immunostimulation and surfactant accumulation.

L9 ANSWER 4 OF 36 MEDLINE
AN 95133154 MEDLINE
DN 95133154
TI Intrachromosomal recombination mediated by the polyomavirus large T antigen.
AU Laurent S; Frances V; Bastin M
CS Department of Biochemistry, University of Sherbrooke, Quebec, Canada..
SO VIROLOGY, (1995 Jan 10) 206 (1) 227-33.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199504
AB We used a spleen necrosis virus-based **retroviral** vector to introduce the polyomavirus replication origin into rat cells and developed a system to analyze **homologous recombination** events that do not reconstitute a selectable marker. Introduction of the gene coding for the polyomavirus large T antigen into the cell lines by DNA transfection promoted high-frequency recombination between the two **retroviral** LTRs, leading to amplification and excision of DNA sequences. To analyze homology requirements, we constructed cell lines carrying only the replication origin without exogenous repeats. Most of the cell lines sustained high-frequency recombination, presumably by undergoing **homologous recombination** between repetitive DNA lying in the vicinity of the integrated origin. Our results indicate that **homologous recombination** promoted by large T antigen does not require recombination hot spots in the viral genome other than the replication origin and they explain the cytotoxicity observed in some cell types when large T antigen is expressed in the presence of a functional origin.

L9 ANSWER 5 OF 36 MEDLINE
AN 95129544 MEDLINE
DN 95129544
TI Concerted evolution of the tandem array encoding primate U2 snRNA occurs in situ, without changing the cytological context of the RNU2 locus.
AU Pavelitz T; Rusche L; Matera A G; Scharf J M; Weiner A M
CS Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine, New Haven, CT 06510.
NC GM31073 (NIGMS)
GM41624 (NIGMS)
SO EMBO JOURNAL, (1995 Jan 3) 14 (1) 169-77.
Journal code: EMB. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
OS GENBANK-L37793; GENBANK-U57614
EM 199504
AB In primates, the tandemly repeated genes encoding U2 small nuclear

RNA evolve concertedly, i.e. the sequence of the U2 repeat unit is essentially homogeneous within each species but differs somewhat between species. Using **chromosome** painting and the NGFR gene as an outside marker, we show that the U2 tandem array (RNU2) has remained at the same **chromosomal** locus (equivalent to human 17q21) through multiple speciation events over > 35 million years leading to the Old World monkey and hominoid lineages. The data suggest that the U2 tandem repeat, once established in the primate lineage, contained sequence elements favoring perpetuation and concerted evolution of the array in situ, despite a pericentric inversion in chimpanzee, a reciprocal translocation in gorilla and a paracentric inversion in orang utan. Comparison of the 11 kb U2 repeat unit found in baboon and other Old World monkeys with the 6 kb U2 repeat unit in humans and other hominids revealed that an ancestral U2 repeat unit was expanded by insertion of a 5 kb **retrovirus** bearing 1 kb long terminal repeats (LTRs). Subsequent excision of the provirus by **homologous recombination** between the LTRs generated a 6 kb U2 repeat unit containing a solo LTR. Remarkably, both junctions between the human U2 tandem array and flanking **chromosomal** DNA at 17q21 fall within the solo LTR sequence, suggesting a role for the LTR in the origin or maintenance of the primate U2 array.

L9 ANSWER 6 OF 36 MEDLINE
AN 94331440 MEDLINE
DN 94331440
TI Characterization of a replication-competent **retrovirus** resulting from recombination of packaging and vector sequences.
AU Otto E; Jones-Trower A; Vanin E F; Stambaugh K; Mueller S N; Anderson W F; McGarrity G J
CS Genetic Therapy Inc., Gaithersburg, MD 20878.
SO HUMAN GENE THERAPY, (1994 May) 5 (5) 567-75.
Journal code: A12. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199411
AB A replication-competent **retrovirus** (RCR) was detected by S+/L- assays in three lots of **retroviral** vector G1Na that were harvested on consecutive days from a single culture of PA317/G1Na producer cells. Using a number of **retrovirus** -specific primer pairs, it was shown that this RCR was a novel recombinant created by exchanges between G1Na and helper sequence pPAM3 and was not an existing RCR introduced by cross-contamination. Sequencing of clones of DNA amplified in six independent PCR reactions confirmed that the 3' portion of this RCR was composed of **retroviral** envelope sequences unique to pPAM3 joined to a 3' long terminal repeat (LTR) unique to G1Na. Comparison of pPAM3 and G1Na sequences at the site corresponding to this junction revealed a short segment of patchy nucleotide identity (8 out of 10 bp), suggesting that these helper and vector sequences were joined by **homologous recombination**. Generation of RCR by exchanges between helper and vector sequences underscores the necessity of testing by efficient methods all **retroviral** vectors for the presence of RCR before their use. Production of 171 lots (855 liters) of various **retroviral** vectors that were free of RCR, including 42 lots of G1Na, however, indicates that the combination of exchanges required to generate an RCR are infrequent in this system.

L9 ANSWER 7 OF 36 MEDLINE
AN 94082449 MEDLINE
DN 94082449
TI Pathogenicity of a subgroup C feline leukemia virus (FeLV) is augmented when administered in association with certain FeLV recombinants.
AU Mathes L E; Pandey R; Chakrabarti R; Hofman F M; Hayes K A; Stromberg P; Roy-Burman P
CS Center for Retrovirus Research, Ohio State University, Columbus 43210.
NC CA51485 (NCI)
T32-CA09320 (NCI)
SO VIROLOGY, (1994 Jan) 198 (1) 185-95.
Journal code: XEA. ISSN: 0042-6822.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 199403
AB There is evidence to suggest that infectious feline leukemia viruses (FeLVs) may be altered biologically because of **homologous recombination** with non-infectious endogenous FeLV (enFeLV) sequences in the infected cells. To evaluate the role of such recombination events in FeLV pathogenesis, a molecular clone of subgroup C FeLV, Sarma strain (FSC), was tested for induction of aplastic anemia in the absence or presence of mixtures of recombinants between FSC and an enFeLV element. In the recombinants, FSC sequences in the viral surface glycoprotein (SU) protein were variably replaced by the corresponding sequences of the enFeLV. The results showed that the virus mixtures varied in their infectivity to neonatal specific pathogen-free cats. One group of mixtures, although exhibiting relatively reduced infectivity, represented the most acute disease-inducing agents. The presence of recombinants in this mixture significantly accelerated the development of erythrocyte aplasia compared to cats infected with FSC alone. In addition, infected cells appeared to be distributed differently in various hematopoietic organs with respect to infection with FSC versus viral mixture. Viral recombinants which were present in this inoculum mixture, however, could not be detected in the plasma or infected tissues of the cats at the end stage of the disease, although their presence in the plasma at the early stages could be detected. Clearly, parental FSC outgrew the recombinants in the infected animals, since its detection was prominent at all stages of the progression of the disease. Therefore, we hypothesize that recombinants initially present in the infected animals, while only poorly replicated compared to FSC in the **host**, might have had the opportunity to infect certain target cells (potentially erythroid progenitor cells) and then disappeared with the associated cytopathic effect.

L9 ANSWER 8 OF 36 MEDLINE
AN 93267761 MEDLINE
DN 93267761
TI Alteration of location of dimer linkage sequence in **retroviral** RNA: little effect on replication or **homologous recombination**.
AU Jones J S; Allan R W; Temin H M
CS McArdle Laboratory for Cancer Research, University of Wisconsin, Madison 53706.

NC CA22[illegible]3 (NCI)
CA071[illegible]5 (NCI)
CA090[illegible]5 (NCI)
SO JOURN[illegible]L OF VIROLOGY, (1993 Jun) 67 (6) 3151-8.
Journ[illegible]l code: KCV. ISSN: 0022-538X.
CY Unit[illegible]d States
DT Journ[illegible]l; Article; (JOURNAL ARTICLE)
LA Engl[illegible]h
FS Prio[illegible]ty Journals; Cancer Journals
EM 1993[illegible]
AB **Retrovirus** particles contain a dimer of **retroviral** genom[illegible]c RNA. A defined region of the **retrovirus** genome has previ[illegible]usly been shown to be important for both dimerization and encap[illegible]idation. To study the importance of the position of this encap[illegible]idation and dimerization signal for **retroviral** repl[illegible]ation and **homologous recombination**, we used [illegible] previously described spleen necrosis virus-based helper cell syst[illegible]m. This system allows **retroviral** vectors with multi[illegible]le genetic markers to be studied after a single cycle of **retroviral** replication. The sequence responsible for dimer[illegible]zation, the encapsidation/dimer linkage sequence (E/DLS), was moved from its normal location near the 5' end of the **retroviral** genome to a location near the 3' end of the genom[illegible]. We characterized four pairs of **retroviral** vectors: (i) [illegible]ith both E/DLSs at the 5' ends of the genomes, (ii) with both E/DL[illegible] at the 3' ends of the genomes, and (iii) two with one E/DLS at th[illegible] 5' end of the genome and one at the 3' end of the genome. We found [illegible]hat moving the E/DLS to the 3' end of the genome resulted in at m[illegible] an approximately factor of 5 reduction in virus titer in a sing[illegible] cycle of **retroviral** replication. Furthermore, we foun[illegible] no changes that were attributable to the alteration of the posi[illegible]on of the E/DLS in the minus-strand DNA primer transfers or the [illegible]us-strand DNA primer transfers, the rate of **homologous recombination**, or the number of internal template switches in r[illegible]combinant proviruses. These results indicate that any alignment or c[illegible]formation necessary for **retroviral** replication or recom[illegible]nation is not the result of the position of the E/DLS.

L9 ANSW[illegible] 9 OF 36 MEDLINE
AN 9325[illegible]40 MEDLINE
DN 93254[illegible]40
TI [Comp[illegible]ete nucleotide sequence of Rous sarcoma virus variants adapted to d[illegible]k cells].
Polna[illegible]a nukleotidnaia posledovatel'nost' adaptirovannogo k kletkam utok[illegible]rianta virusa sarkomy rausa.
AU Kash[illegible]a V I; Kavsan V M; Ryndich A V; Lazurkevich Z V; Zubak S V; Popo[illegible] V; Dostalova V; Glozhanek I
SO MOLE[illegible]KARNAIA BIOLOGIIA, (1993 Mar-Apr) 27 (2) 436-50.
Jour[illegible] code: NGX. ISSN: 0026-8984.
CY RUSS[illegible] Russian Federation
DT Jour[illegible]; Article; (JOURNAL ARTICLE)
LA Russ[illegible]
FS Prio[illegible]ty Journals
EM 1993
AB Subg[illegible]p C avian sarcoma viruses efficiently infect and transform but [illegible]ly replicate in duck cells. Nucleotide sequence analysis of Prag[illegible] strain of Rous sarcoma virus adapted by numerous passages on duck [illegible]broblasts (daPr-RSV-C) showed that adaptation of orig[illegible]lly chicken virus to duck cells correlated with changes in viral [illegible]enome, first of all in gp85-coding domain of env-gene.

Besi changes in LTR and src-gene sequences could play a role in wide . of host range for this virus. The major changes of d. -RSV-C in comparison with original Pr-RSV-C appeared to be the . ult of homologous recombinations with corr. onding regions of chicken endogenous retroviruses.

L9 ANSW .0 OF 36 MEDLINE
AN 9207 MEDLINE
DN 9207 .
TI The . persion of defective endogenous murine retroviral elem. . suggests retrotransposition-mediated amplification.
AU Fred. m M; Policastro P F; Wilson M C
CS Scrip. Research Institute, Department of Molecular Biology and Neur. armacology, La Jolla, CA 92037.
NC CA 3. 0 (NCI)
CA 0 . (NCI)
SO DNA . CELL BIOLOGY, (1991 Dec) 10 (10) 713-22.
Jour. code: AF9. ISSN: 1044-5498.
CY Unit tates
DT Jour. Article; (JOURNAL ARTICLE)
LA Engl.
FS Prio. y Journals
EM 1992
AB The persion of four replication-defective endogenous proviruses, orig. ly detected in 129 strain mice and shown to have extensive dele. ns of gag, pol, and env gene regions, was investigated in 13 inbr. strains and substrains of mice. Using probes to sequences flan. the integration sites in 129 mice, unique genomic Eco RI frag. ts were assigned to each of the four endogenous proviral elem. s. Analyses revealed that certain of these proviral elements are p. sent both in strains closely related to strain 129 (i.e., stra. s 101 and LP/J) and in more distantly related strains (i.e., stra. BALB/cJ, A/J, and C3H/HeJ). In mouse strains lacking prov. integration at a particular locus, the size of the cor. nding Eco RI genomic fragment and absence of a char. ristic Kpn I site indicated the lack of a residual solitary long. minal repeat. Hybridization of oligonucleotide probes that dist. ish the specific deletions present within these elements iden. ed additional analogous proviral integrations at many diff. t sites in all strains investigated. These data indicate that . diversification of these proviral elements found in inbred stra. s generated by integration of new copies, rather than exci. through homologous recombination. More the results are consistent with other endogenous retr. uses providing the trans-acting proteins necessary to p. ge the defective viral RNA.

=> d 11-2 b ab

L9 ANSW 1 OF 36 MEDLINE
AN 9007 MEDLINE
DN 9007
TI Homo gous recombination between the LTRs of a huma. retrovirus-like element causes a 5-kb deletion in two . ings.
AU Mage. ; Goodchild N L
CS Ter. x Laboratory, British Columbia Cancer Research Centre, Univ. ty of British Columbia, Vancouver, Canada..
SO AMER. JOURNAL OF HUMAN GENETICS, (1989 Dec) 45 (6) 848-54.

Jour code: 3IM. ISSN: 0002-9297.
CY Unit tates
DT Jou Article; (JOURNAL ARTICLE)
LA Engl
FS Pric Journals
EM 199(
AB The -H family of human endogenous **retrovirus**-like
elem consists of approximately 1,000 intact members and of a
simi number of solitary long terminal repeats (LTRs). In this
stuc ne genetic heterogeneity of these elements has been
inve ited using unique flanking probes isolated from cDNA clones
cont ng RTVL-H sequences. Four such probes were used to screen a
pane human DNA samples for genetic differences. One of these
prob etected a 5.0-kb deletion in two related individuals.
Clor and DNA hybridization analysis indicated that the nondeleted
comm llele contained an intact RTVL-H element, whereas the
dele variant allele contained only a single LTR. DNA sequence
comp ons strongly suggest that the deletion is due to
homologous recombination between the 5' and 3'
LTRs the RTVL-H sequence. This is the first reported case of a
DNA ation in humans that is due to an LTR-LTR excision event.

L9 ANSW 2 OF 36 MEDLINE
AN 893(MEDLINE
DN 893(
TI Pros s for correction of thalassemia by genetic engineering.
AU Gale
CS Depa t of Medicine, UCLA School of Medicine 90024.
NC CA2(NCI)
SO PROC IN CLINICAL AND BIOLOGICAL RESEARCH, (1989) 309 141-59.
Ref:
Jou code: PZ5. ISSN: 0361-7742.
CY Unit ates
DT Jou Article; (JOURNAL ARTICLE)
Gene eview; (REVIEW)
(REV TUTORIAL)
LA Engl
FS Pric Journals
EM 198(
AB The assemias are diverse genetic disorders characterized by
abnc synthesis rates of one or more proteins constituting
hemc n (globin-chains). In the beta-thalassemias, genes encoding
the -globin chain are intact but are abnormally transcribed or,
less n, translated. In the alpha-thalassemias, genes encoding
the -globin chain are often deleted; abnormal transcription can
alsc r. The human beta- and alpha-globin genes were molecularly
clor This review considers attempts to introduce these genes in
mamm n cells by physical techniques such as **chromosome**
trar transfection, fusion, micro-injection, electroporation and
homc s **recombination** or by using DNA or RNA
viru such as **retroviruses**. Currently, inefficient gene
expr n in **host** cells and the need for precise cognate
regu n of globin gene expression are the major limitations to
appl genetic engineering to thalassemia.

L9 ANSW OF 36 MEDLINE
AN 892(MEDLINE
DN 892(
TI Gene geting with **retroviral** vectors: recombination by
gene ersion into regions of nonhomology.

AU Ell[illegible] Bernstein A
CS Dep[illegible] t of Medical Genetics, University of Toronto, Ontario, Can[illegible]
SO MOL[illegible] AND CELLULAR BIOLOGY, (1989 Apr) 9 (4) 1621-7. Jou[illegible] ode: NGY. ISSN: 0270-7306.
CY Unit[illegible] ates
DT Jou[illegible] Article; (JOURNAL ARTICLE)
LA Engl[illegible]
FS Pric[illegible] Journals
EM 198[illegible]
AB We [illegible] esigned and constructed integration-defective **retro**[illegible]al vectors to explore their potential for gene targ[illegible] in mammalian cells. Two nonoverlapping deletion mutants of the [illegible]rial neomycin resistance (neo) gene were used to detect **hom**[illegible]s **recombination** events between viral and **chro**[illegible]mal sequences. Stable neo gene correction events were[illegible]ected at a frequency of approximately 1 G418r cell per 3 x 10([illegible]fected cells. Analysis of the functional neo gene in ind[illegible]nt targeted cell clones indicated that unintegrated **retr**[illegible]al linear DNA recombined with the target by gene con[illegible]n for variable distances into regions of nonhomology. In add[illegible] transient neo gene correction events which were associated with[illegible] complete loss of the **chromosomal** target sequences were[illegible]rved. These results demonstrated that **retroviral** vec[illegible]an recombine with homologous **chromosomal** seq[illegible]s in rodent and human cells.

L9 ANS[illegible] OF 36 MEDLINE
AN 892[illegible] MEDLINE
DN 892[illegible]
TI Act[illegible]n of the c-H-ras proto-oncogene by **retrovirus** ins[illegible] and **chromosomal** rearrangement in a Moloney leu[illegible] virus-induced T-cell leukemia.
AU Ihl[illegible] Smith-White B; Sisson B; Parker D; Blair D G; Schultz A; Koz[illegible] Lunsford R D; Askew D; Weinstein Y; et al
CS Mol[illegible] Mechanisms of Carcinogenesis Laboratory, National Cancer Ins[illegible]-Frederick, Cancer Research Facility, Maryland 21701.
NC NO1-[illegible]101 (NCI) CA2[illegible] NCI)
SO JOU[illegible] VIROLOGY, (1989 Jul) 63 (7) 2959-66. Jou[illegible]ode: KCV. ISSN: 0022-538X.
CY Uni[illegible]ates
DT Jou[illegible] Article; (JOURNAL ARTICLE)
LA Eng[illegible]
FS Pri[illegible] Journals; Cancer Journals
OS GEN[illegible]27193
EM 198[illegible]
AB A r[illegible]gement of the c-H-ras locus was detected in a T-cell line (DA-[illegible]tablished from a Moloney leukemia virus-induced tumor. This rea[illegible]ment was associated with the high-level expression of H-ras RNA [illegible]he H-ras gene product, p21. DNA from DA-2 cells transformed fib[illegible]sts in DNA transfection experiments, and the transformed fib[illegible]sts contained the rearranged H-ras locus. The rearrangement inv[illegible] one allele and was present in tissue from the primary tumor fro[illegible]h the cell line was isolated. Cloning and sequencing of the rea[illegible]d allele and comparison with the normal allele demonstrated tha[illegible]earrangement was complex and probably resulted from the int[illegible]n of a **retrovirus** in the H-ras locus between a 5' [illegible]ng exon and the first coding exon and a subsequent **hom**[illegible]s **recombination** between this provirus and

ano· ewly acquired provirus also located on **chromosome**
7. ' events resulted in the translocation of the coding exons of
the locus away from the 5' noncoding exon region to a new
gen· ite on **chromosome** 7. Sequencing of the coding
reg: f the gene failed to detect mutations in the 12th, 13th,
59t! 61st codons. The possible reasons for the complexity of the
rea. ment and the significance of the activation of the H-ras
loc: T-cell transformation are discussed.

L9 ANS OF 36 MEDLINE
AN 881. MEDLINE
DN 881.
TI Rec· tion between two integrated proviruses, one of which was
ins· near c-myc in a **retrovirus**-induced rat thymoma:
imp. ons for tumor progression.
AU Laz· Tsichlis P N
CS Fox Cancer Center, Philadelphia, Pennsylvania 19111.
NC CA-· (NCI)
CA-· (NCI)
RR-· (NCRR)
SO JOU· F VIROLOGY, (1988 Mar) 62 (3) 788-94.
Jou: ode: KCV. ISSN: 0022-538X.
CY Uni· ates
DT Jou Article; (JOURNAL ARTICLE)
LA Eng.
FS Pri· Journals; Cancer Journals
OS GEN· I9096
EM 198·
AB Of · oney murine leukemia virus (MoMuLV)-induced rat thymomas, 2
con· rearrangement in c-myc. In one of these tumors the
obs· rearrangement was not due to the insertion of an intact
MoM· ovirus. The rearranged c-myc DNA fragment from this thymoma
was · and examined by restriction endonuclease mapping,
hyb· tion to MoMuLV proviral DNA probes, and DNA sequence
ana. These analyses revealed that the c-myc rearrangement in
thi· was due to the presence of a partially duplicated MoMuLV
lon· inal repeat (LTR) 5' to c-myc exon 1. The orientation of
thi· structure was opposite to the transcriptional orientation
of · The sequences at the 3' flanking side of the LTR structure
were ved from a cellular DNA region which maps to the same
chro· me as c-myc (chro**mosome** 7), although to a
site · ant from this proto-oncogene. These findings present
evi· for a **homologous recombination** event
occ· between sequences of two proviruses integrated on the same
chr· me, one of which was inserted near the c-myc
pro· ogene. The recombination product contains three copies of
the ' LTR 72-base-pair direct repeat and is associated with a
hig· of c-myc expression. The reciprocal product of this
rec· ion was not detected. We propose that recombination
bet· mologous sequences may play a significant role in the
gen· of **chromosomal** rearrangements and therefore in
tum· uction and progression.

L9 ANS OF 36 MEDLINE
AN 852 MEDLINE
DN 852·
TI Str· and biological activity of human homologs of the raf/mil
onc·
AU Bon· ; Kerby S B; Sutrave P; Gunnell M A; Mark G; Rapp U R
SO MOL· AND CELLULAR BIOLOGY, (1985 Jun) 5 (6) 1400-7.

Jou de: NGY. ISSN: 0270-7306.
CY Uni tes
DT Jou rticle; (JOURNAL ARTICLE)
LA Eng
FS Pri Journals
OS GEN L1376; GENBANK-L00213; GENBANK-L00206; GENBANK-L00207;
GEN L0208; GENBANK-L00209; GENBANK-L00210; GENBANK-L00211;
GEN L00212; GENBANK-M11377
EM 198
AB Two genes homologous to the raf/mil oncogene have been cloned
and ced. One, c-raf-2, is a processed pseudogene; the other,
c-r contains nine exons homologous to both raf and mil and two
add l exons homologous to mil. A 3' portion of c-raf-1
con g six of the seven amino acid differences relative to
mur af can substitute for the 3' portion of v-raf in a
tra tion assay. Sequence homologies between c-raf-1 and
Mol ukemia virus at both ends of v-raf indicate that the viral
gen cquired by **homologous recombination**.
Alt he data are consistent with the traditional model of
ret l transduction, they also raise the possibility
tha ransduction occurred in a double crossover event between
pro NA and the murine gene.

L9 ANS OF 36 MEDLINE
AN 851 MEDLINE
DN 851
TI Rec ion between a defective **retrovirus** and
hom s sequences in **host** DNA: reversion by patch
rep
AU Sch erg P; Colicelli J; Goff S P
NC CA NCI)
SO JOU VIROLOGY, (1985 Mar) 53 (3) 719-26.
Jou de: KCV. ISSN: 0022-538X.
CY Uni tes
DT Jou rticle; (JOURNAL ARTICLE)
LA Eng
FS Pri Journals; Cancer Journals
OS GEN 3364; GENBANK-M17738
EM 198
AB The s of mammalian species contain multiple copies of
seq homologous to exogenous **retroviruses**. When a
mut rovirus carrying a lethal deletion in an
ess viral gene was introduced into mammalian cells, revertant
vir peared and spread throughout the culture. Analysis of one
suc tant showed that the mutation had been repaired by
hom s **recombination** with endogenous
seq . Our results suggest that defective **retroviruses**
can pon the genetic complement of the **host** cell to
rep ions in viral genes.

L9 ANS OF 36 MEDLINE
AN 850 MEDLINE
DN 850
TI Nuc cid sequences of the oncogene v-rel in
ret dotheliosis virus strain T and its cellular homolog, the
pro gene c-rel.
AU Wil K C; Eggleton K; Temin H M
NC CA- NCI)
CA- NCI)
CA- NCI)

SO JOU ' VIROLOGY, (1984 Oct) 52 (1) 172-82.
Jou de: KCV. ISSN: 0022-538X.
CY Uni tes
DT Jou rticle; (JOURNAL ARTICLE)
LA Eng
FS Pri ournals; Cancer Journals
OS GEN 537; GENBANK-K00555; GENBANK-K02447; GENBANK-K02448;
GEN 449; GENBANK-K02450; GENBANK-K02451; GENBANK-K02452;
GEN 453; GENBANK-K02454; GENBANK-K02455
EM 198
AB Ret dotheliosis virus strain T (Rev-T) is a highly oncogenic
rep n-defective **retrovirus** which contains the
onc -rel. It is thought that Rev-T arose when a virus similar
to the helper virus of Rev-T, infected a turkey and
rec with c-rel from that turkey. There is one large c-rel
loc he turkey genome which contains all of the sequences
hom to v-rel (K. C. Wilhelmsen and H. M. Temin, J. Virol.
49: , 1984). We have sequenced v-rel and its flanking
seq each of the regions of the c-rel locus from turkey that
are gous to v-rel and their flanking sequences, and the coding
seq or env and part of pol of Rev-A. The v-rel coding
seq can be translated into a 503-amino acid
env out-of-frame-env fusion polypeptide. We have not detected
any ces in the Los Alamos or University of California-San
Die bases that are more significantly related to the amino
aci leic acid sequence of v-rel than to the randomized
seq f v-rel. Comparison of Rev-A, Rev-T, and c-rel indicates
tha -rel sequences may have been transduced from the c-rel
(tu ocus by a novel mechanism. There are sequences in Rev-A
and that are similar to splicing signals, indicating that the
5' rel junction of Rev-T may have been formed by cellular RNA
spl achinery. Eight presumed introns have presumably been
spl of c-rel to generate v-rel. There are also short
imp regions of homology between sequences at the boundaries of
v-r sequences in Rev-A and c-rel (turkey), indicating that
c-r have been transduced by **homologous**
rec **tion**. There are many differences between the amino
aci nces of the predicted translational products of v-rel and
c-r h may account for their difference in transformation
pot . These sequence differences between v-rel and c-rel
inc missense transitions, four missense transversions, and
thr es where Rev-T has a small in-frame deletion of sequences
rel c-rel. Most of the coding sequence differences between
c-r -rel are nonconservative amino acid changes.

L9 ANS OF 36 MEDLINE
AN 842 MEDLINE
DN 842
TI Rec ion of transfected DNAs in vertebrate cells in culture.
AU Ban ay P K; Watanabe S; Temin H M
NC CA- ICI)
CA- ICI)
SO PRC OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES
OF . (1984 Jun) 81 (11) 3476-80.
Jou le: PV3. ISSN: 0027-8424.
CY Uni tes
DT Jou rticle; (JOURNAL ARTICLE)
LA Eng
FS Pri ournals; Cancer Journals
EM 198

AB We the frequency of homologous and illegitimate
rec ions between transfected noninfectious **retroviral**
DNA les in chicken embryo fibroblasts. The frequency of
rec ion was determined by the formation of infectious virus
and with the extent of homology between the DNA molecules at
the recombination, but only when there were regions of
hom urrounding this region. While **homologous**
rec **tion** led to the formation of wild-type virus,
ill te recombination resulted in formation of infectious virus
wit ations at the site of recombination. Apparent
hom **recombination** was also observed between
tra d and **chromosomal** DNAs in D17 dog cells.

L9 ANS OF 36 MEDLINE
AN 840 MEDLINE
DN 840
TI Int osomal recombination of the cellular oncogene c-myc with
the globulin heavy chain locus in murine plasmacytomas is a
rec exchange.
AU Cor rondakis S; Adams J M
NC CA (CI)
SO EMB AL, (1983) 2 (5) 697-703.
Jou le: EMB. ISSN: 0261-4189.
CY ENG nited Kingdom
DT Jou rticle; (JOURNAL ARTICLE)
LA Eng
FS Pri ournals
EM 198
AB The chromosome translocations found in most murine
pla mas involve the cellular gene (c-myc) homologous to the
onc -myc) of avian **retrovirus** MC29, Translocation
lin c-myc gene of **chromosome** 15 to the
imm ulin heavy (H) chain locus of **chromosome** 12,
oft in the switch recombination (S) region 5' to the alpha
con egion (C alpha) gene. We have investigated c-myc
rea ents in 21 BALB/c plasmacytomas and three B lymphomas by
Sou lot analysis. We show that the t(15;12) is a reciprocal
chr exchange since most tumours contain not only a
c-m linked to the S alpha C alpha region but also a separate
str ith S mu or S alpha linked to the c-myc 5'-flanking
rec alysis of the two rearrangement products cloned from
pla ma J558 suggests that one type of H locus target for
tra ion is an S alpha region recombined with S mu; two other
tar pear to be other switched heavy chain genes and an
unr ed C alpha gene. Nearly all the **chromosome** 15
bre fall within a 1.1-kb region spanning a 5' c-myc exon;
hen sion of the transcriptional unit by translocation can
acc the altered c-myc transcription in plasmacytomas. The
c-m point region lacks substantial homology with S mu or S
alp uing against **homologous recombination**
as nslocation mechanism.

=> logof

ALL L# S ND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? LD:y

COST IN LARS	SINCE FILE ENTRY	TOTAL SESSION
FULL EST OST	19.11	19.26

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